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(54) **Title:** 1-AMINO 1H-IMIDAZOQUINOLINES

(57) **Abstract:** 1-Amino 1H-imidazoquinoline compounds, pharmaceutical compositions containing the compounds, intermediates, and methods of making and methods of use of these compounds as immunomodulators, for modulating cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

1-AMINO 1*H*-IMIDAZOQUINOLINES

FIELD OF THE INVENTION

This invention relates to 1-amino 1*H*-imidazoquinoline compounds, pharmaceutical compositions containing such compounds, intermediates used in their preparation, and the use of these compounds as immunomodulators.

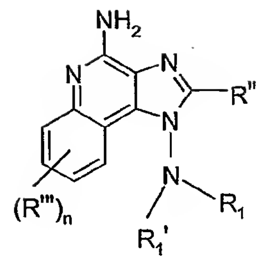
BACKGROUND OF THE INVENTION

There has been a major effort in recent years to find compounds that modulate the immune system. Examples of such compounds, which have demonstrated cytokine inducing and immunomodulating activity, are disclosed by U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,352,784; 5,389,640; 5,446,153; 5,482,936; 5,494,916; 5,756,747; 6,110,929; 6,194,425; 6,331,539; 6,376,669; 6,451,810; 6,525,064; 6,541,485; 6,545,016; 6,545,017; 6,656,938; 6,660,735; 6,660,747; 6,664,260; 6,664,264; 6,664,265; 6,667,312; 6,670,372; 6,677,347; 6,677,348; and 6,683,088.

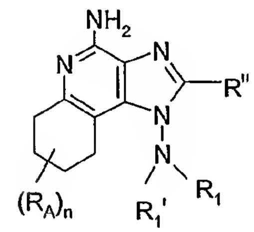
But despite important progress in the effort to find immunomodulating compounds, there is still a critical scientific and medical need for additional compounds that have an ability to modulate aspects of the immune response, by induction of cytokine biosynthesis or other mechanisms.

SUMMARY OF THE INVENTION

It has now been found that certain 1-amino 1*H*-imidazoquinoline compounds modulate cytokine biosynthesis. In one aspect, the present invention provides compounds of the Formulas I and II:

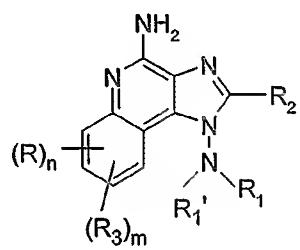


I

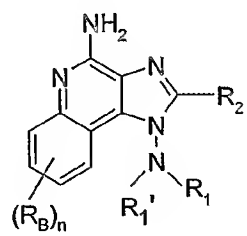


II

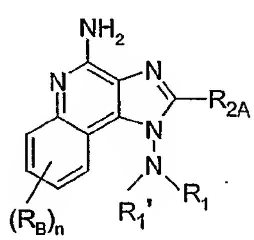
and more specifically the following compounds of the Formulas I-1, I-2, I-3, and II-1:



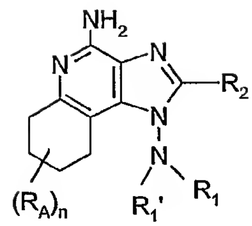
I-1



I-2



I-3



II-1

wherein R_1', R_1, R_2, R_{2A}, R_3, R'', R''', R, R_A, R_B, n and m are as defined below; and pharmaceutically acceptable salts thereof.

The compounds of Formulas I, I-1, I-2, I-3, II, and II-1 are useful as immune response modifiers (IRMs) due to their ability to modulate cytokine biosynthesis (e.g., induce or inhibit the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. Compounds can be tested per the test procedures described in the Examples Section. Compounds can be tested for induction of cytokine biosynthesis by incubating human PBMC in a culture with the compound(s) at a concentration range of 30 to 0.014 μM and analyzing for interferon (α) or tumor necrosis factor (α) in the culture supernatant. Compounds can be tested for inhibition of cytokine biosynthesis by incubating mouse macrophage cell line Raw 264.7 in a culture with the compound(s) at a single concentration of, for example, 5 μM and analyzing for tumor necrosis factor (α) in the culture supernatant. The ability to modulate cytokine biosynthesis, for example, induce the biosynthesis of one or more cytokines, makes the compounds useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

In another aspect, the present invention provides pharmaceutieal compositions containing the immune response modifier compounds, and methods of inducing eytokine biosynthesis in animal cells, treating a viral disease in an animal, and/or treating a neoplastic disease in an animal by administering to the animal one or more compounds of the Formulas I, I-1, I-2, I-3, II, and/or II-1, and/or pharmaceutically acceptable salts thereof.

In another aspect, the invention provides methods of synthesizing the compounds of Formulas I, I-1, I-2, I-3, II, and II-1 and intermediates useful in the synthesis of these compounds.

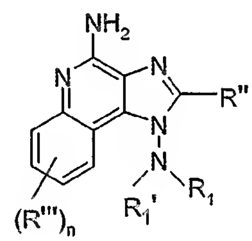
As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In eaeh instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

In one aspect, the present invention provides 1-amino 1*H*-imidazoquinoline compounds of the following Formula I:



I

wherein:

R_1' is selected from the group consisting of hydrogen and alkyl;

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

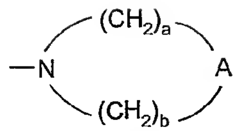
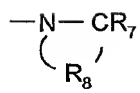
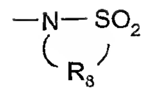
-X-R_5,

-X-N(R_6)-Y-R_4,

-X-C(R_7)-N(R_6)-R_4, and

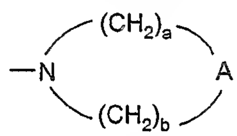
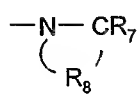
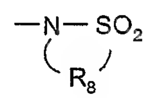
-X-O-R_4;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:

 ,  , and  ;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of:

 ,  , and  ;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

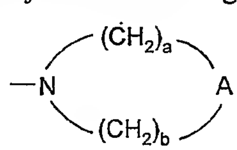
R_7 is selected from the group consisting of =O and =S;

R_8 is C_{2-7} alkylene;

A is selected from the group consisting of $-CH(R_6)-$, $-O-$, $-N(R_6)-$, $-N(Y-R_4)-$, and $-N(X-N(R_6)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from the group consisting of $-C(R_7)-$, $-C(R_7)-O-$, $-S(O)_2-$, $-S(O)_2-N(R_6)-$, and $-C(R_7)-N(R_9)-$; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group

 ;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_6)-, -N(Y-R_4)-, or -N(X-N(R_6)-Y-R_4)- then a and b are independently integers from 2 to 4;

each R" is independently hydrogen or a non-interfering substituent;

each R"' is independently a non-interfering substituent; and

n is an integer from 0 to 4;

or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula I, R" is selected from the group consisting of:

- -hydrogen,
- -alkyl,
- -alkenyl,
- -aryl,
- -heteroaryl,
- -heterocyclyl,
- -alkylene-Z-alkyl,
- -alkylene-Z-aryl,
- -alkylene-Z-alkenyl, and
- -alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
    - -OH,
    - -halogen,
    - -N(R_6)$_2$,
    - -C(R_7)-N(R_6)$_2$,
    - -S(O)$_2$-N(R_6)$_2$,
    - -N(R_6)-C(R_7)-C_{1-10} alkyl,
    - -N(R_6)-S(O)$_2$-C_{1-10} alkyl,
    - -C(O)-C_{1-10} alkyl,
    - -C(O)-O-C_{1-10} alkyl,
    - -N_3,
    - -aryl,
    - -heteroaryl,
    - -heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

each R_7 is independently selected from the group consisting of =O and =S; and

Z is selected from the group consisting of -O- and -$S(O)_{0-2}$-.

In some embodiments of Formula I, R''' is R or R_3 when n is 1, R or one R and one R_3 when n is 2, or R when n is 3 to 4; wherein:

R is selected from the group consisting of alkyl, alkenyl, alkoxy, halogen, fluoroalkyl, hydroxy, amino, alkylamino, and dialkylamino;

R_3 is selected from the group consisting of:

-Z'-R_4',

-Z'-X'-R_4',

-Z'-X'-Y'-R_4', and

-Z'-X'-R_5';

Z' is a bond or -O-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene, or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_{11})$-,

-$C(R_7)$-,

-$C(R_7)$-O-,

-O-$C(R_7)$-,

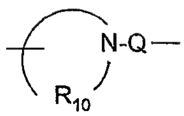
-O-C(O)-O-,

-$N(R_{11})$-Q-,

-$C(R_7)$-$N(R_{11})$-,

-O-$C(R_7)$-$N(R_{11})$-,

-$C(R_7)$-$N(OR_{12})$-,



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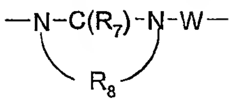

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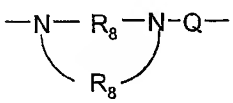

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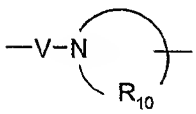

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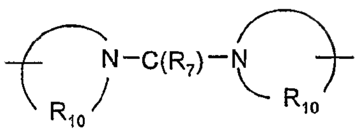
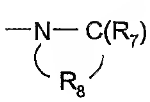
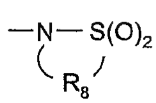
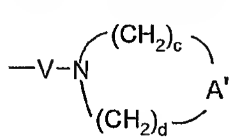
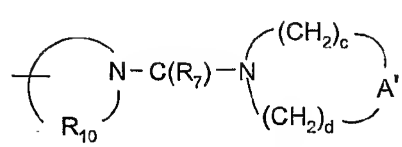


;

R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5' is selected from the group consisting of:

 ,  ,  , and  ;

each R_7 is independently selected from the group consisting of =O and =S;

each R_8 is independently C_{2-7} alkylene;

R_{10} is C_{3-8} alkylene;

each R_{11} is independently selected from the group consisting of hydrogen,

C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxyC_{2-10} alkylenyl, and arylC_{1-10} alkylenyl;

R_{12} is selected from the group consisting of hydrogen and alkyl;

A' is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4')-$;

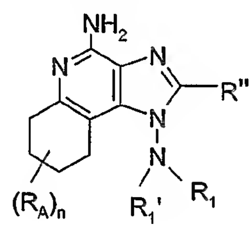
Q is selected from the group consisting of a bond, $-C(R_7)-$, $-C(R_7)-C(R_7)-$, $-S(O)_2-$, $-C(R_7)-N(R_{11})-W-$, $-S(O)_2-N(R_{11})-$, $-C(R_7)-O-$, and $-C(R_7)-N(OR_{12})-$;

V is selected from the group consisting of $-C(R_7)-$, $-O-C(R_7)-$, $-N(R_{11})-C(R_7)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7, and when A' is -O- or $-N(R_4')-$ then c and d are independently integers from 2 to 4.

The present invention also provides 1-amino 6,7,8,9-tetrahydro 1*H*-imidazoquinoline compounds of the following Formula II:



II

wherein:

each R_A is independently selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio,

$-NH_2$,

-NH(alkyl), and

$-N(alkyl)_2$;

n is an integer from 0 to 4;

R_1' is selected from the group consisting of hydrogen and alkyl;

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

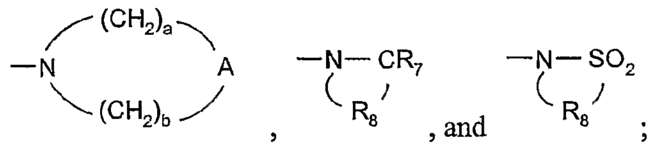
$-X-R_5$,

$-X-N(R_6)-Y-R_4$,

$-X-C(R_7)-N(R_6)-R_4$, and

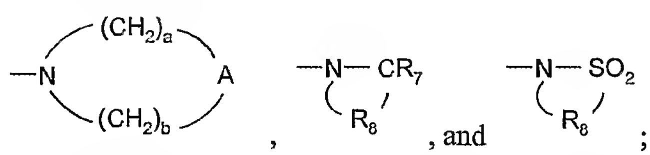
$-X-O-R_4$;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

R_7 is selected from the group consisting of =O and =S;

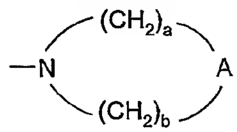
R_8 is C_{2-7} alkylene;

A is selected from the group consisting of $-CH(R_6)-$, $-O-$, $-N(R_6)-$, $-N(Y-R_4)-$, and

-N(X-N(R_6)-Y-R_4)-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_7)-, -C(R_7)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_6)-, and -C(R_7)-N(R_9)-; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group



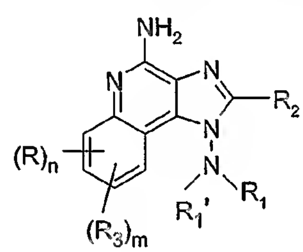
;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_6)-, -N(Y-R_4)-, or -N(X-N(R_6)-Y-R_4)- then a and b are independently integers from 2 to 4; and

R" is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

The present invention also provides compounds of the following Formula I-1:



I-1

wherein:

R_1' is selected from the group consisting of hydrogen and alkyl;

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

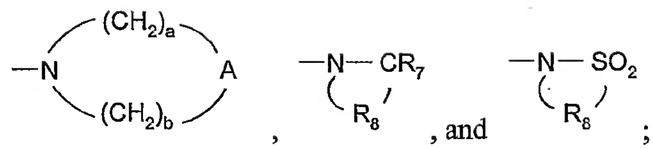
-X-R_5,

-X-N(R_6)-Y-R_4,

-X-C(R_7)-N(R_6)-R_4, and

-X-O-R_4;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

$-N(R_6)_2$,

$-C(R_7)-N(R_6)_2$,

$-S(O)_2-N(R_6)_2$,

$-N(R_6)-C(R_7)-C_{1-10}$ alkyl,

$-N(R_6)-S(O)_2-C_{1-10}$ alkyl,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

-aryl,

-heteroaryl,

-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

R_3 is selected from the group consisting of:

$-Z'-R_4'$,

-Z'-X'-R_4',

-Z'-X'-Y'-R_4', and

-Z'-X'-R_5';

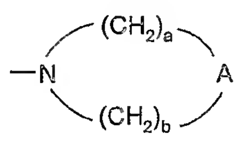
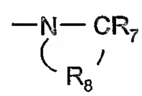
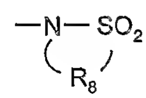
each R is independently selected from the group consisting of alkyl, alkenyl, alkoxy, halogen, fluoroalkyl, hydroxy, amino, alkylamino, and dialkylamino;

n is an integer from 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

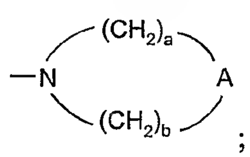
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of:

 ,  , and  ;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_7)-, -C(R_7)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_6)-, and -C(R_7)-N(R_9)-; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group

 ;

Z is selected from the group consisting of -O- and -S(O)$_{0-2}$-;

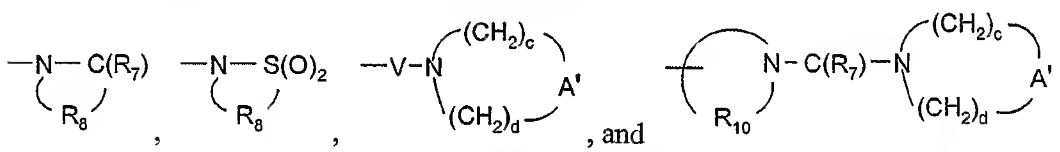
A is selected from the group consisting of -CH(R_6)-, -O-, -N(R_6)-, -N(Y-R_4)-, and

$-N(X-N(R_6)-Y-R_4)-$;

a and b are independently integers from 1 to 4 with the proviso that when A is $-O-$, $-N(R_6)-$, $-N(Y-R_4)-$, or $-N(X-N(R_6)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5' is selected from the group consisting of:



X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene, or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_{11})-$,

$-C(R_7)-$,

$-C(R_7)-O-$,

$-O-C(R_7)-$,

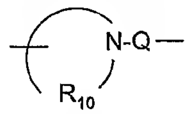
$-O-C(O)-O-$,

$-N(R_{11})-Q-$,

$-C(R_7)-N(R_{11})-$,

-O-C(R_7)-N(R_{11})-,

-C(R_7)-N(OR_{12})-,



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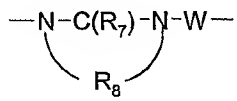

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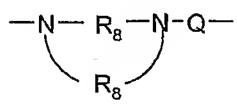

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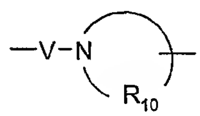
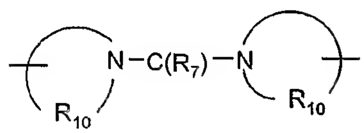


, and



;

Z' is a bond or -O-;

A' is selected from the group consisting of $-CH_2$-, -O-, -C(O)-, $-S(O)_{0-2}$-, and -N(R_4')-;

Q is selected from the group consisting of a bond, -C(R_7)-, -C(R_7)-C(R_7)-, $-S(O)_2$-, -C(R_7)-N(R_{11})-W-, $-S(O)_2$-N(R_{11})-, -C(R_7)-O-, and -C(R_7)-N(OR_{12})-;

V is selected from the group consisting of -C(R_7)-, -O-C(R_7)-, -N(R_{11})-C(R_7)-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

c and d are independently integers from 1 to 6 with the proviso that $c + d$ is ≤ 7, and when A' is -O- or -N(R_4')- then c and d are independently integers from 2 to 4;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

each R_7 is independently selected from the group consisting of =O and =S;

each R_8 is independently C_{2-7} alkylene;

R_{10} is C_{3-8} alkylene;

each R_{11} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxyC_{2-10} alkylenyl, and arylC_{1-10} alkylenyl; and

R_{12} is selected from the group consisting of hydrogen and alkyl; or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula I-1, R_1 is selected from the group consisting of $-R_4$, $-Y-R_4$, and $-X-N(R_6)-Y-R_4$ wherein Y is $-C(R_7)-$, $-S(O)_2-$, or $-C(R_7)-N(R_9)-$.

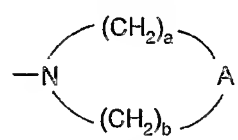
In certain embodiments of Formula I-1, R_1 is selected from the group consisting of hydrogen, alkyl, alkenyl, arylalkylenyl, arylalkenylenyl, heteroarylalkylenyl, heteroarylalkenylenyl, aminoalkylenyl, alkoxyalkylenyl, acyl, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylaminocarbonyl, arylaminocarbonyl, (arylalkylenyl)aminoalkylenyl, and arylaminocarbonylaminoalkylenyl.

In certain embodiments of Formula I-1, R_1 is selected from the group consisting of hydrogen, methyl, isopropyl, butyl, 2-methylpropyl, 1-ethylpropyl, 3-methylbutyl, cyclohexyl, benzyl, 3-phenylpropyl, cinnamyl, furan-2-ylmethyl, and $-CH_2CH_2CH_2-NHR_{13}$, wherein R_{13} is selected from the group consisting of methanesulfonyl, phenylsulfonyl, benzyl, isopropylaminocarbonyl, and phenylaminoearbonyl.

In some embodiments of Formula I-1, R_1' is hydrogen.

In some embodiments of Formula I-1, R_1 and R_1' are each independently alkyl.

In some embodiments of Formula I-1, R_1 and R_1' join to form the group:



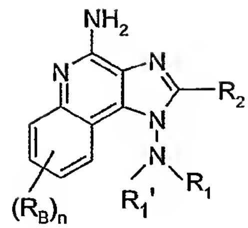
.

In some embodiments of Formula I-1, R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl, and in certain embodiments R_2 is selected from the group eonsisting of hydrogen, methyl, propyl, butyl, 2-methoxyethyl, and ethoxymethyl.

In some embodiments of Formula I-1, n is 0.

In some embodiments of Formula I-1, n is 0, and R_3 is selected from the group consisting of $-Z'-R_4'$, $-Z'-X'-R_4'$, and $-Z'-X'-Y'-R_4'$, and in certain embodiments R_3 is selected from the group consisting of 2-(pyridin-3-yl)ethyl, pyridinyl, hydroxymethylpyridinyl, ethoxyphenyl, (morpholine-4-carbonyl)phenyl, 2-(methanesulfonylamino)ethoxy, and benzyloxy.

The present invention also provides compounds of the following Formula (I-2):



I-2

wherein:

R_B is selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

n is an integer from 0 to 4;

R_1' is selected from the group consisting of hydrogen and alkyl;

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

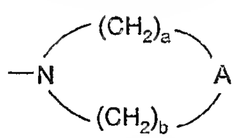
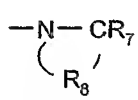
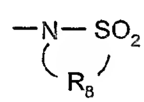
-X-R_5,

-X-N(R_6)-Y-R_4,

-X-C(R_7)-N(R_6)-R_4, and

-X-O-R_4;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:

 ,  , and  ;

R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

$-N(R_6)_2$,

$-C(R_7)-N(R_6)_2$,

$-S(O)_2-N(R_6)_2$,

$-N(R_6)-C(R_7)-C_{1-10}$ alkyl,

$-N(R_6)-S(O)_2-C_{1-10}$ alkyl,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

-aryl,

-heteroaryl,

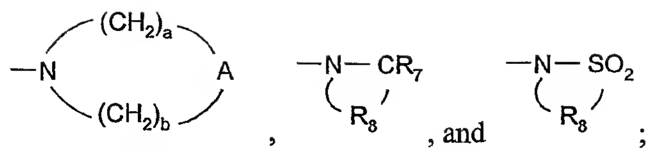
-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

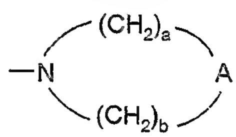
each R_7 is independently selected from the group consisting of =O and =S;

R_8 is C_{2-7} alkylene;

A is selected from the group consisting of $-CH(R_6)-$, -O-, $-N(R_6)-$, $-N(Y-R_4)-$, and $-N(X-N(R_6)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from the group consisting of $-C(R_7)-$, $-C(R_7)-O-$, $-S(O)_2-$, $-S(O)_2-N(R_6)-$, and $-C(R_7)-N(R_9)-$; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group



;

Z is selected from the group consisting of -O- and $-S(O)_{0-2}-$; and

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, $-N(R_6)-$, $-N(Y-R_4)-$, or $-N(X-N(R_6)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula I-2, R_1 is selected from the group consisting of $-R_4$, $-Y-R_4$, and $-X-N(R_6)-Y-R_4$ wherein Y is $-C(R_7)-$, $-S(O)_2-$, or $-C(R_7)-N(R_9)-$.

In certain embodiments of Formula I-2, R_1 is selected from the group consisting of hydrogen, alkyl, alkenyl, arylalkylenyl, arylalkenylenyl, heteroarylalkylenyl, heteroarylalkenylenyl, aminoalkylenyl, alkoxyalkylenyl, acyl, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylaminocarbonyl, arylaminocarbonyl, (arylalkylenyl)aminoalkylenyl, and arylaminocarbonylaminoalkylenyl.

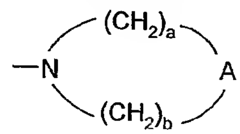
In certain embodiments of Formula I-2, R_1 is selected from the group consisting of hydrogen, methyl, isopropyl, butyl, 2-methylpropyl, 1-ethylpropyl, 3-methylbutyl,

cyclohexyl, benzyl, cinnamyl, furan-2-ylmethyl, and $-CH_2CH_2CH_2-NHR_{13}$, wherein R_{13} is selected from the group consisting of methanesulfonyl, phenylsulfonyl, benzyl, and phenylaminocarbonyl.

In some embodiments of Formula I-2, R_1' is hydrogen.

In some embodiments of Formula I-2, R_1 and R_1' are each independently alkyl.

In some embodiments of Formula I-2, R_1 and R_1' join to form the group:

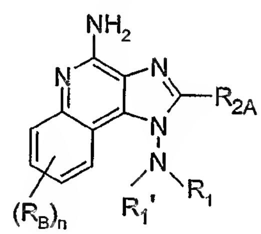


In some embodiments of Formula I-2, R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl, and in certain embodiments R_2 is selected from the group consisting of hydrogen, butyl, 2-methoxyethyl, and ethoxymethyl.

In some embodiments of Formula I-2, n is 0.

In some embodiments of Formula I-2, n is 1, and R is halogen or hydroxy.

The present invention also provides compounds of the following Formula (I-3):



I-3

wherein:

R_B is selected from alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

n is an integer from 0 to 4;

R_1' is selected from hydrogen and alkyl;

R_1 is selected from:

$-R_4$,

$-Y-R_4$,

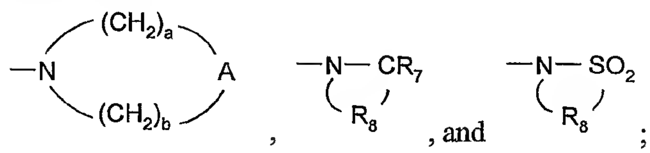
$-X-R_5$,

$-X-N(R_6)-Y-R_4$,

$-X-CR_7-N(R_6)-R_4$, and

$-X-O-R_4$;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from:



R_{2A} is selected from:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z- alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from:

-OH,

-halogen,

$-N(R_6)_2$,

$-CR_7-N(R_6)_2$,

$-SO_2-N(R_6)_2$,

$-N(R_6)-CR_7-C_{1-10}$ alkyl,

$-N(R_6)- SO_2-C_{1-10}$ alkyl,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

-aryl,

-heteroaryl,

-heterocyclyl,

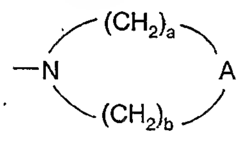
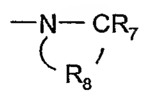
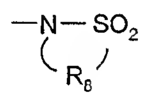
-C(O)-aryl, and

-C(O)-heteroaryl;

R_4 is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups

can be unsubstituted or substituted by one or more substituents independently selected from alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two earbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from:

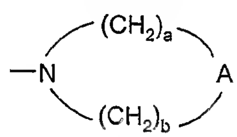
 ,  , and  ;

R_6 is selected from hydrogen, alkyl, and arylalkylenyl;

R_7 is selected from =O and =S;

R_8 is C_{2-7} alkylene;

R_9 is selected from hydrogen, alkyl, and arylalkylenyl, or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group

 ;

A is selected from $-CHR_6-$, -O-, $-N(R_6)-$, $-N(Y-R_4)-$, and $-N(X-N(R_6)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from $-CR_7-$, $-SO_2-$, $-SO_2-N(R_6)-$, and $-CR_7-N(R_9)-$;

Z is selected from -O- and $-S(O)_{0-2}-$;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, $-N(R_6)-$, $-N(Y-R_4)-$, or $-N(X-N(R_6)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

and pharmaceutically acceptable salts thereof.

In some embodiments of Formula I-3, R_1 is selected from $-R_4$, $-Y-R_4$, and $-X-N(R_6)-Y-R_4$ wherein Y is $-CR_7-$, $-SO_2-$, or $-CR_7-N(R_9)-$.

In certain embodiments of Formula I-3, R_1 is selected from the group consisting of hydrogen, alkyl, alkenyl, arylalkylenyl, arylalkenylenyl, heteroarylalkylenyl,

heteroarylalkenylenyl, aminoalkylenyl, alkoxyalkylenyl, acyl, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylaminocarbonyl, arylaminocarbonyl, (arylalkylenyl)aminoalkylenyl, and arylaminocarbonylaminoalkylenyl.

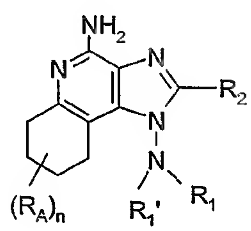
In certain embodiments of Formula I-3, R_1 is selected from hydrogen, isopropyl, butyl, cyclohexyl, benzyl, cinnamyl, and $-CH_2CH_2CH_2-NHR_{13}$, wherein R_{13} is selected from methanesulfonyl, phenylsulfonyl, benzyl, and phenylaminocarbonyl.

In some embodiments of Formula I-3, R_1' is hydrogen.

In some embodiments of Formula I-3, R_{2A} is selected from hydrogen, alkyl, and alkoxyalkylenyl, and in certain embodiments R_{2A} is selected from hydrogen, butyl, methoxyethyl (e.g., 2-methoxyethyl), and ethoxymethyl.

In some embodiments of Formula I-3, n is 0.

The present invention also provides compounds of the following Formula (II-1):



II-1

wherein:

each R_A is independently selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio,

$-NH_2$,

-NH(alkyl), and

-N(alkyl)$_2$;

n is an integer from 0 to 4;

R_1' is selected from the group consisting of hydrogen and alkyl;

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

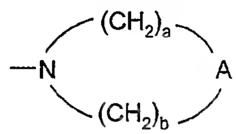
-X-R_5,

-X-N(R_6)-Y-R_4,

-X-C(R_7)-N(R_6)-R_4, and

-X-O-R_4;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



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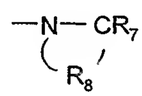
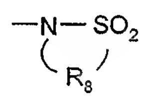


, and


;

R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

-N(R_6)$_2$,

-C(R_7)-N(R_6)$_2$,

-S(O)$_2$-N(R_6)$_2$,

-N(R_6)-C(R_7)-C_{1-10} alkyl,

-N(R_6)-S(O)$_2$-C_{1-10} alkyl,

-C(O)-C_{1-10} alkyl,

-C(O)-O-C_{1-10} alkyl,

-N_3,

-aryl,

-heteroaryl,

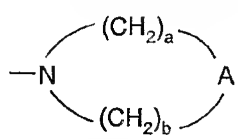
-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of:



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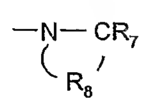

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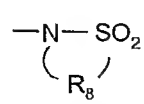


;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

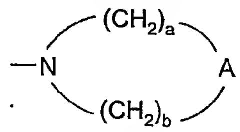
each R_7 is independently selected from the group consisting of =O and =S;

R_8 is C_{2-7} alkylene;

A is selected from the group consisting of -CH(R_6)-, -O-, -N(R_6)-, -N(Y-R_4)-, and -N(X-N(R_6)-Y-R_4)-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of $-C(R_7)-$, $-C(R_7)-O-$, $-S(O)_2-$, $-S(O)_2-N(R_6)-$, and $-C(R_7)-N(R_9)-$; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group



;

Z is selected from the group consisting of -O- and $-S(O)_{0-2}-$; and

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, $-N(R_6)-$, $-N(Y-R_4)-$, or $-N(X-N(R_6)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula II-1, R_1 is selected from the group consisting of $-R_4$, $-Y-R_4$, and $-X-N(R_6)-Y-R_4$ wherein Y is $-C(R_7)-$, $-S(O)_2-$, or $-C(R_7)-N(R_9)-$.

In certain embodiments of Formula II-1, R_1 is selected from the group consisting of hydrogen, alkyl, alkenyl, arylalkylenyl, arylalkenylenyl, heteroarylalkylenyl, heteroarylalkenylenyl, aminoalkylenyl, alkoxyalkylenyl, acyl, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylaminocarbonyl, arylaminocarbonyl, (arylalkylenyl)aminoalkylenyl, and arylaminocarbonylaminoalkylenyl.

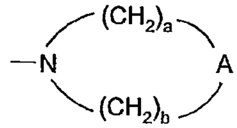
In certain embodiments of Formula II-1, R_1 is selected from the group consisting of hydrogen, methyl, isopropyl, butyl, 2-methylpropyl, 1-ethylpropyl, 3-methylbutyl, cyclohexyl, benzyl, cinnamyl, furan-2-ylmethyl, and $-CH_2CH_2CH_2-NHR_{13}$, wherein R_{13} is selected from the group consisting of methanesulfonyl, phenylsulfonyl, benzyl, and phenylaminocarbonyl.

In certain embodiments of Formula II-1, R_1 is selected from the group consisting of hydrogen, methyl, isopropyl, butyl, 2-methylpropyl, 1-ethylpropyl, 3-methylbutyl, cyclohexyl, benzyl, 3-phenylpropyl, cinnamyl, furan-2-ylmethyl, and $-CH_2CH_2CH_2-NHR_{13}$, wherein R_{13} is selected from the group consisting of methanesulfonyl, phenylsulfonyl, benzyl, isopropylaminocarbonyl, and phenylaminocarbonyl.

In some embodiments of Formula II-1, R_1' is hydrogen.

In some embodiments of Formula II-1, R_1 and R_1' are each independently alkyl.

In some embodiments of Formula II-1, R_1 and R_1' join to form the group:

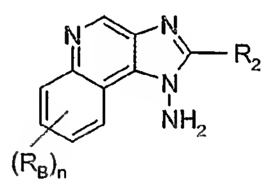


In some embodiments of Formula II-1, R_2 is selected from the group eonsisting of hydrogen, alkyl, and alkoxyalkylenyl, in certain embodiments R_2 is selected from the group consisting of hydrogen, butyl, 2-methoxyethyl, and ethoxymethyl, and in certain embodiments R_2 is selected from the group consisting of hydrogen, methyl, propyl, butyl, 2-methoxyethyl, and ethoxymethyl.

In some embodiments of Formula II-1, n is 0.

The present invention also provides compounds that are useful as intermediates in the synthesis of compounds of Formula I, I-1, I-2, I-3, II, and/or II-1. These intermediate compounds have the structural Formulas VII, IX, X, XLII, and XLIII described below.

The present invention provides intermediate compounds of the following Formula (VII):



VII

wherein:

eaeh R_B is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

n is an integer from 0 to 4;

R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

$-N(R_6)_2$,

$-C(R_7)-N(R_6)_2$,

$-S(O)_2-N(R_6)_2$,

$-N(R_6)-C(R_7)-C_{1-10}$ alkyl,

$-N(R_6)- S(O)_2-C_{1-10}$ alkyl,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

-aryl,

-heteroaryl,

-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

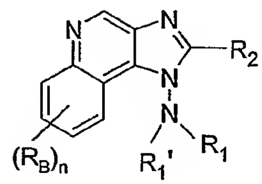
each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

R_7 is selected from the group consisting of =O and =S; and

Z is selected from the group consisting of -O- and $-S(O)_{0-2}-$;

or a pharmaceutically acceptable salt thereof.

The present invention also provides intermediate compounds of the following Formula (IX):



IX

wherein:

each R_B is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

n is an integer from 0 to 4;

R_1' is hydrogen or alkyl;

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

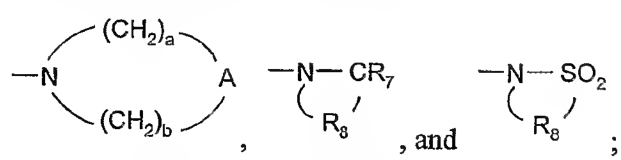
-X-R_5,

-X-N(R_6)-Y-R_4,

-X-C(R_7)-N(R_6)-R_4, and

-X-O-R_4;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

$-N(R_6)_2$,

$-C(R_7)-N(R_6)_2$,

$-S(O)_2-N(R_6)_2$,

$-N(R_6)-C(R_7)-C_{1-10}$ alkyl,

$-N(R_6)- S(O)_2-C_{1-10}$ alkyl,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

-aryl,

-heteroaryl,

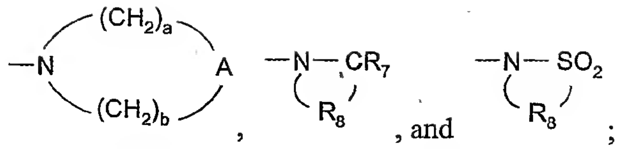
-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of



each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

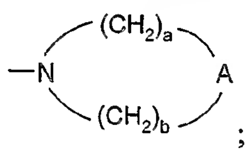
each R_7 is independently selected from the group consisting of =O and =S;

R_8 is C_{2-7} alkylene;

A is selected from the group consisting of -CH(R_6)-, -O-, -N(R_6)-, -N(Y-R_4)-, and -N(X-N(R_6)-Y-R_4)-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_7)-, -C(R_7)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_6)-, and -C(R_7)-N(R_9)-; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group

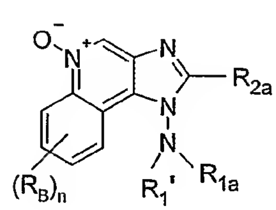


Z is selected from the group consisting of -O- and -S(O)$_{0-2}$-; and

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_6)-, -N(Y-R_4)-, or -N(X-N(R_6)-Y-R_4)- then a and b are independently integers from 2 to 4;

or a pharmaceutically acceptable salt thereof.

The present invention also provides intermediate compounds of the following Formula (X):



X

wherein:

each R_B is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

n is an integer from 0 to 4;

R_1' is hydrogen or alkyl;

R_{1a} is selected from the group consisting of:

-R_{4a},

-Y-R_{4a},

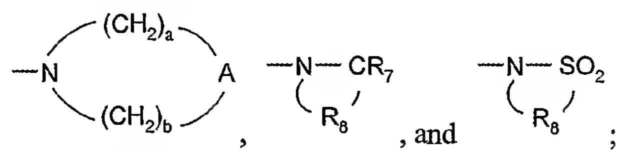
-X-R_5,

-X-N(R_6)-Y-R_{4a},

-X-C(R_7)-N(R_6)-R_{4a}, and

-X-O-R_{4a};

or R_1' and R_{1a} together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



R_{2a} is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-alkylene-Z"-alkyl,

-alkylene-Z"-aryl,

-alkylene-Z"- alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

-N(R_6)$_2$,

-C(R_7)-N(R_6)$_2$,

-S(O)$_2$-N(R_6)$_2$,

-N(R_6)-C(R_7)-C_{1-10} alkyl,

-N(R_6)- S(O)$_2$-C_{1-10} alkyl,

-C(O)-C_{1-10} alkyl,

-C(O)-O-C_{1-10} alkyl,

-N_3,

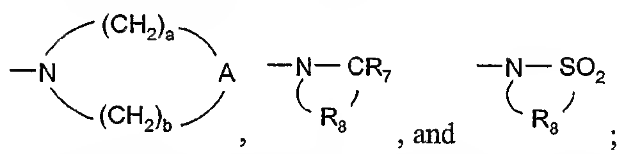
-aryl,

-heterocyclyl, and

-C(O)-aryl;

R_{4a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_{4a} is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of



each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

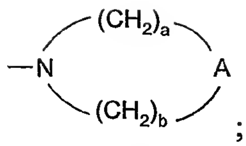
each R_7 is independently selected from the group consisting of =O and =S;

R_8 is C_{2-7} alkylene;

A is selected from the group consisting of -CH(R_6)-, -O-, -N(R_6)-, -N(Y-R_4)-, and -N(X-N(R_6)-Y-R_4)-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_7)-, -C(R_7)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_6)-, and -C(R_7)-N(R_9)-; wherein R_9 is selected from the group consisting of hydrogen, alkyl and arylalkylenyl, or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group

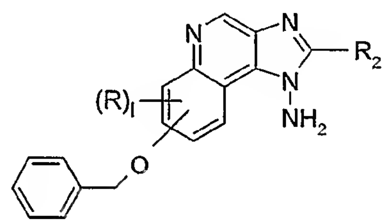


Z" is selected from the group consisting of -O- and $-S(O)_2-$; and

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, $-N(R_6)-$, $-N(Y-R_4)-$, or $-N(X-N(R_6)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

or a pharmaceutically acceptable salt thereof.

The present invention also provides intermediate compounds of the following Formula (XLII):



XLII

wherein:

R is selected from the group consisting of alkyl, alkenyl, alkoxy, halogen, fluoroalkyl, hydroxy, amino, alkylamino, and dialkylamino;

l is 0 or 1;

R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

$-N(R_6)_2$,

$-C(R_7)-N(R_6)_2$,

$-S(O)_2-N(R_6)_2$,

$-N(R_6)-C(R_7)-C_{1-10}$ alkyl,

$-N(R_6)-S(O)_2-C_{1-10}$ alkyl,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

-aryl,

-heteroaryl,

-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

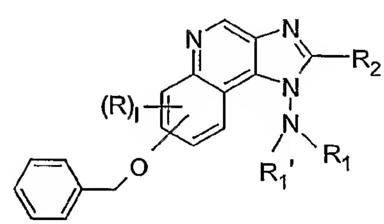
each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

R_7 is selected from the group consisting of =O and =S; and

Z is selected from the group consisting of -O- and $-S(O)_{0-2}-$;

or a pharmaceutically acceptable salt thereof.

The present invention also provides intermediate compounds of the following Formula (XLIII):



XLIII

wherein:

R is selected from the group consisting of alkyl, alkenyl, alkoxy, halogen, fluoroalkyl, hydroxy, amino, alkylamino, and dialkylamino;

l is 0 or 1;

R_1' is hydrogen or alkyl;

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

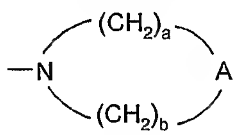
-X-R_5,

-X-N(R_6)-Y-R_4,

-X-C(R_7)-N(R_6)-R_4, and

-X-O-R_4;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



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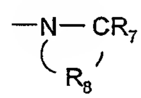
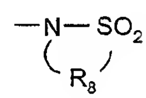


, and


;

R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

-N(R_6)$_2$,

-C(R_7)-N(R_6)$_2$,

-S(O)$_2$-N(R_6)$_2$,

-N(R_6)-C(R_7)-C_{1-10} alkyl,

-N(R_6)- S(O)$_2$-C$_{1-10}$ alkyl,

-C(O)-C$_{1-10}$ alkyl,

-C(O)-O-C$_{1-10}$ alkyl,

-N$_3$,

-aryl,

-heteroaryl,

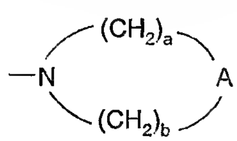
-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of



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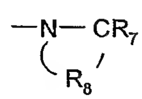
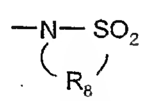


, and


;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

each R_7 is independently selected from the group consisting of =O and =S;

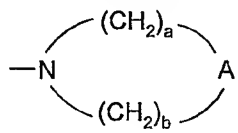
R_8 is C$_{2-7}$ alkylene;

A is selected from the group consisting of -CH(R_6)-, -O-, -N(R_6)-, -N(Y-R_4)-, and -N(X-N(R_6)-Y-R_4)-;

X is C$_{2-20}$ alkylene;

Y is selected from the group consisting of -C(R_7)-, -C(R_7)-O-, -S(O)$_2$-,

$-S(O)_2-N(R_6)-$, and $-C(R_7)-N(R_9)-$; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group


;

Z is selected from the group consisting of -O- and $-S(O)_{0-2}-$; and

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, $-N(R_6)-$, $-N(Y-R_4)-$, or $-N(X-N(R_6)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

or a pharmaceutically acceptable salt thereof.

Herein, "non-interfering" means that the ability of the compound or salt to modulate (e.g., induce or inhibit) the biosynthesis of one or more cytokines is not destroyed by the non-interfering substitutent. Illustrative non-interfering R" groups include those described above for R_2 in Formulas I-1, I-2, and II-1, and for R_{2A} in Formula I-3. Illustrative non-interfering R''' groups include those described above for R and R_3 in Formula I-1, and for R_B in Formulas I-2 and I-3.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. Likewise, "alkylenyl," "alkenylenyl," and "alkynylenyl" are the divalent forms of the "alkyl,"

"alkenyl," and "alkynyl" groups defined above. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term “haloalkyl” is inclusive of alkyl groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix “halo-”. Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like. Similarly, the term "fluoroalkyl" is inclusive of groups that are substituted by one or more fluorine atoms, including perfluorinated groups (e.g., trifluoromethyl).

The term “aryl” as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

The term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl, homopiperazinyl, and the like.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. Likewise, "arylenyl," "heteroarylenyl," and "heterocyclylenyl" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group or substituent is present more that once in any Formula described herein, each group or substituent is independently selected, whether specifically stated or not.

The invention is inclusive of the compounds described herein and salts thereof in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

Preparation of the Compounds

Compounds of the invention can be prepared according to Reaction Scheme I wherein R, R_{1a}, R_{2a}, and n are as defined above.

In step (1) of Reaction Scheme I, a 4-chloro-3-nitroquinoline of Formula III is reacted with *tert*-butyl carbazate or an alternate carbazate to provide a carbazate compound of Formula IV. The reaction can be carried out by adding *tert*-butyl carbazate to a solution of a compound of Formula III in a suitable solvent such as anhydrous dichloromethane in the presence of a base such as triethylamine. The reaction can be run at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods. Many compounds of Formula III are known or can be prepared using known synthetic methods, see for example, U.S. Patent Nos. 4,689,338; 5,175,296; 5,367,076; and 5,389,640; and the documents cited therein. *Tertiary*-butyl carbazate is commercially available (for example, from Aldrich, Milwaukee, WI). Many alternate carbazate reagents (for example, benzyl carbazate) may be prepared using known synthetic methods.

In step (2) of Reaction Scheme I a carbazate compound of Formula IV is reduced to provide a compound of Formula V. The reduction can be carried out using a conventional heterogeneous hydrogenation catalyst such as platinum on carbon or palladium on carbon. For some compounds of Formula IV, for example, compounds in which R is halogen, a platinum catalyst is preferred. The reaction can be conveniently carried out on a Parr apparatus in a suitable solvent such as toluene and/or isopropanol. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Other reduction processes may be used for the reduction in step (2). For example, an aqueous solution of sodium dithionite can be added to a solution or suspension of the

compound of Formula IV in a suitable solvent such as ethanol or isopropanol. The reaction can be carried out at an elevated temperature, for example at reflux, or at ambient temperature.

In step (3) of Reaction Scheme I a compound of Formula V is (i) reacted with an acyl halide of Formula $R_{2a}C(O)Cl$ or $R_{2a}C(O)Br$ and then (ii) cyclized to provide a 1*H*-imidazo compound of Formula VI. In part (i) the acyl halide is added to a solution of a compound of Formula V in a suitable solvent such as anhydrous dichloromethane in the presence of a base such as triethylamine. The reaction can be run at a reduced temperature, for example, 0° C, or at ambient temperature. In part (ii) the product of part (i) is heated in an alcoholic solvent in the presence of a base. For example, the product of part (i) is refluxed in ethanol in the presence of excess triethylamine or is heated with methanolic ammonia.

Alternatively, step (3) can be carried out by reacting a compound of Formula V with a carboxylic acid or an equivalent thereof. Suitable equivalents to carboxylic acid include orthoesters and 1,1-dialkoxyalkyl alkanoates. The earboxylic acid or equivalent is selected such that it will provide the desired R_{2a} substituent in a compound of Formula VI. For example, triethyl orthoformate will provide a compound where R_{2a} is hydrogen, and triethyl orthovalerate will provide a compound where R_{2a} is butyl. The reaction can be run in the absence of solvent or in an inert solvent such as anhydrous toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be included. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (4) of Reaction Scheme I, the *tert*-butoxycarbonyl or alternate oxyearbonyl group is removed from a 1*H*-imidazo compound of Formula VI by hydrolysis under acidic conditions to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula VIIa or a salt (for example, hydrochloride salt) thereof. For example, a compound of Formula VI is dissolved in 1.5M HCl in ethanol and heated to reflux. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (5a) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula VIIa or a salt thereof is treated with a ketone, aldehyde, or corresponding ketal or acetal thereof, under acidic conditions to provide a compound of Formula VIII. For

example, a ketone is added to a solution of the hydrochloride salt of a compound of Formula VIIa in a suitable solvent such as isopropanol in the presence of an acid or acid resin, for example, DOWEX W50-X1 acid resin. The ketone, aldehyde, or corresponding ketal or acetal thereof, is selected with R_i and R_{ii} groups that will provide the desired R_{1a} substituent in a 1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula IXa. For example, acetone will provide a compound where R_{1a} is isopropyl, and benzaldehyde will provide a compound where R_{1a} is benzyl. The reaction is run with sufficient heating to drive off the water formed as a byproduct of the reaction. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (6) of Reaction Scheme I, a compound of Formula VIII is reduced to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula IXa. The reaction can be carried out by adding sodium borohydride to a solution of a compound of Formula VIII in a suitable solvent, for example, methanol. The reaction can be run at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Alternatively, in step (5b) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula VIIa can be treated with a ketone and a borohydride under acidic conditions to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula IXa. For example, the hydrochloride salt of a 1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula VIIa, dissolved in a suitable solvent such as 1,2-dichloroethane, can be treated with a ketone and sodium triacetoxyborohydride at room temperature. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

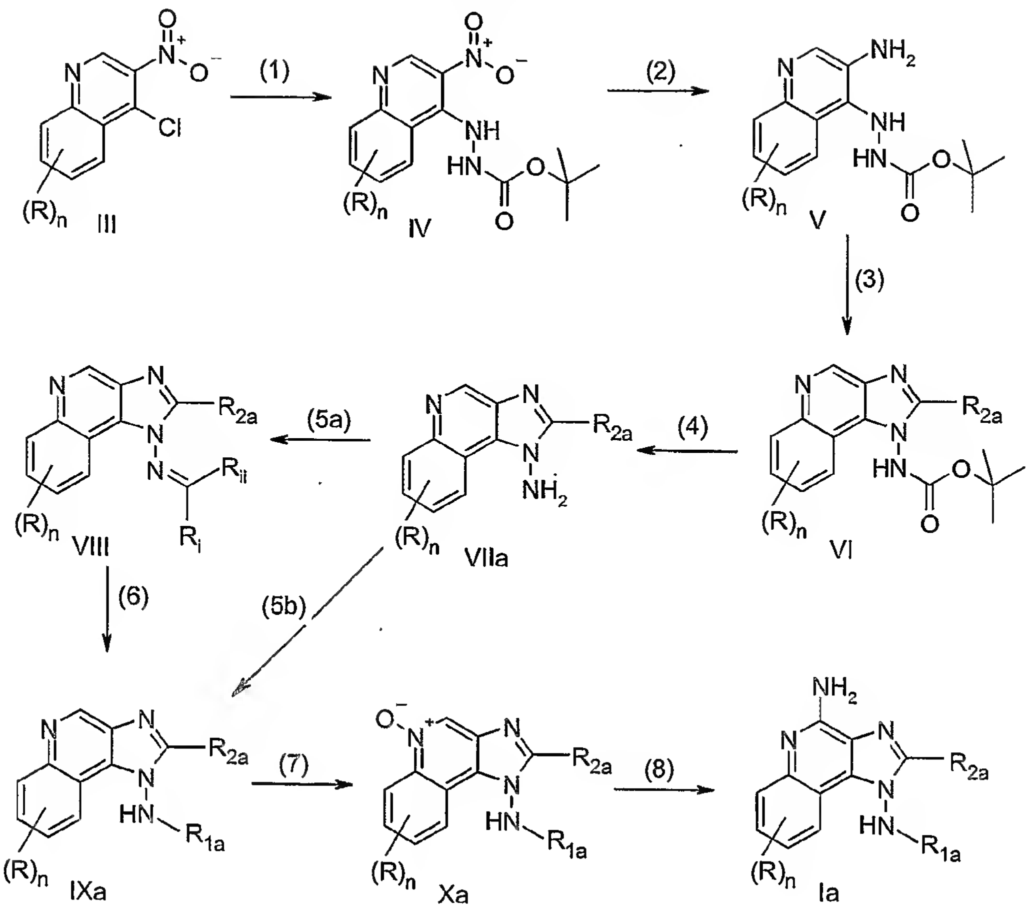
In step (7) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula IXa is oxidized to provide an *N*-oxide of Formula Xa using a conventional oxidizing agent that is capable of forming *N*-oxides. The reaction is carried out by treating a solution of a compound of Formula IXa in a suitable solvent such as chloroform or dichloromethane with 3-chloroperoxybenzoic acid at ambient temperature. The product or a pharmaceutieally acceptable salt thereof can be isolated by conventional methods.

In step (8) of Reaction Scheme I, an N-oxide of Formula Xa is aminated to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula Ia, which is a subgenus of compounds of the Formulas I, I-1, I-2, and I-3. The reaction is carried out in two parts. In part (i) a compound of Formula Xa is reacted with an acylating agent. Suitable acylating

agents include alkyl- or arylsulfonyl chorides (e.g., benzenesulfonyl choride, methanesulfonyl choride, and *p*-toluenesulfonyl chloride). In part (ii) the product of part (i) is reacted with an excess of an aminating agent. Suitable aminating agents include ammonia (e.g. in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium bicarbonate, ammonium phosphate). The reaction can be carried out by dissolving a compound of Formula Xa in a suitable solvent such as dichloromethane, adding ammonium hydroxide to the solution, and then adding *p*-toluenesulfonyl chloride. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Alternatively, the oxidation of step (7) and the amination of step (8) can be carried out sequentially without isolating the product of the oxidation to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula Ia. In step (7), after the 1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula IXa is consumed by reaction with 3-chloroperoxybenzoic acid as described in step (7), the aminating and acylating agents are added to the reaction mixture as in step (8). The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme I



Compounds of the invention can be prepared according to Reaction Scheme II wherein R, R_1, R_{2a} and n are as defined above.

In step (1) of Reaction Scheme II, a 1*H*-imidazo compound of Formula VI is oxidized to provide an *N*-oxide of Formula XI using the method of step (7) in Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (2) of Reaction Scheme II, an *N*-oxide of Formula XI is aminated using the method of step (8) in Reaction Scheme I to provide a 4-amino compound of the Formula XIIa. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

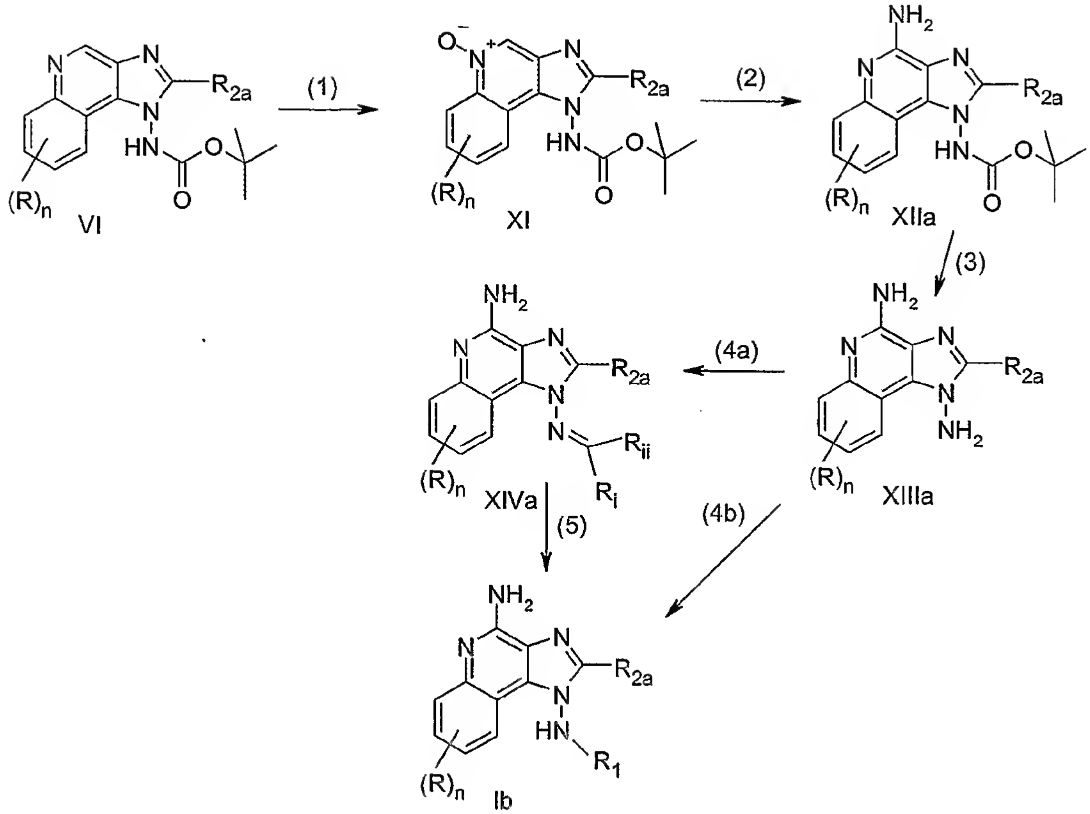
In step (3) of Reaction Scheme II, the *tert*-butoxycarbonyl or alternate oxycarbonyl group is removed from a 4-amino compound of the Formula XIIa using the method of step (4) in Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula XIIIa or a salt (for example, hydrochloride salt) thereof. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (4a) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula XIIIa is treated with a ketone, aldehyde, or corresponding ketal or acetal thereof, using the method of step (5a) in Reaction Scheme I to provide a compound of Formula XIVa. The ketone, aldehyde, or corresponding ketal or acetal thereof, is selected with R_i and R_{ii} groups that will provide the desired R_1 substituent in a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine compound of Formula Ib. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (5) of Reaction Scheme II, a compound of Formula XIVa is reduced to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula Ib using the method of step (6) in Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Alternatively, in step (4b) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula XIIIa can be treated with a ketone and a borohydride using the method of step (5b) of Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula Ib, which is a subgenus of compounds of the Formulas I, I-1, I-2, and I-3. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme II

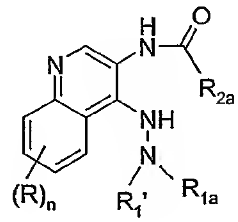


Compounds of the invention can be prepared according to Reaction Scheme III wherein R, R_1', R_{1a}, R_{2a}, and n are as defined above.

In step (1) of Reaction Scheme III, a 4-chloro-3-nitroquinoline of Formula III is reacted with a hydrazino compound of Formula XVa to provide a compound of Formula XVI. The reaction can be carried out by adding the hydrazino compound of Formula XVa to a solution of a compound of Formula III in a suitable solvent such as anhydrous dichloromethane in the presence of a base such as triethylamine. The reaction can be run at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods. Many hydrazino compounds of Formula XVa are commercially available; others can be readily prepared using known synthetic methods.

In step (2) of Reaction Scheme III, a compound of Formula XVI is reduced to provide a compound of Formula XVII using the methods of step (2) in Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (3) of Reaction Scheme III, a compound of formula XVII is cyclized using the methods of step (3) in Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula IXb. The product of step (i) (described in step (3) of Reaction Scheme I) can be isolated to provide a compound of the following formula:



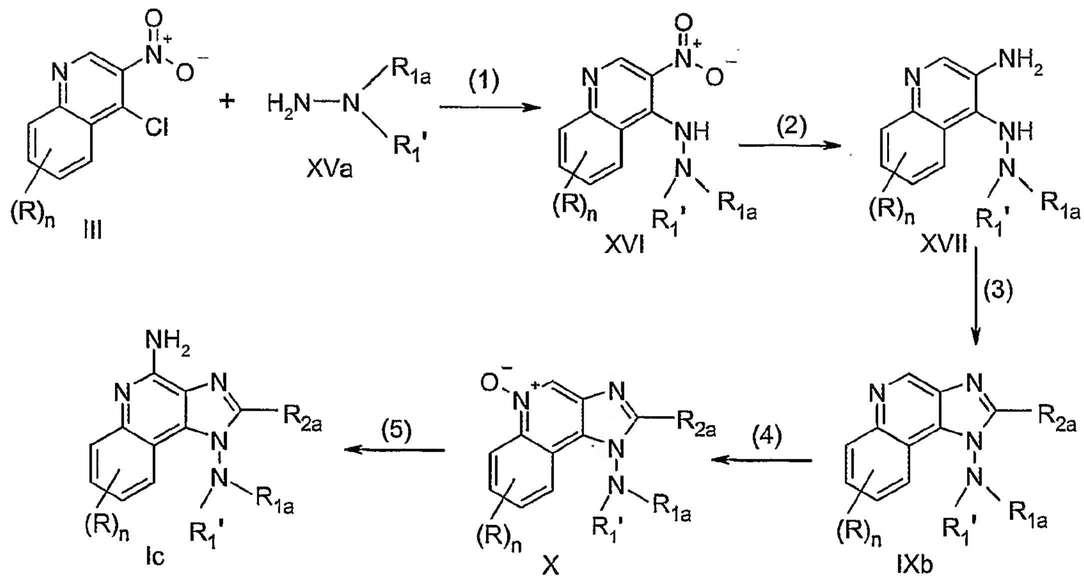
In part (ii) the product of part (i) can be refluxed in suitable solvent such as toluene in the presence of pyridine hydrochloride. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (4) of Reaction Scheme III, a 1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula IXb is oxidized to provide an *N*-oxide of Formula X using the method of step (7) in Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (5) of Reaction Scheme III, an *N*-oxide of Formula X is aminated using the method of step (8) in Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula Ic, which is a subgenus of compounds of the Formulas I, I-1, I-2, and I-3. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Alternatively, the oxidation of step (4) and the amination of step (5) can be carried out sequentially without isolating the product of the oxidation to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula Ic. In step (4), after the 1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula IXb is consumed by reaction with 3-chloroperoxybenzoic acid as described in step (4), the aminating and aeylating agents are added to the reaction mixture as in step (5). The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme III



Compounds of the invention can be prepared according to Reaction Scheme IV wherein R, R_1, R_2 and n are as defined above.

In step (1) of Reaction Scheme IV, a 2,4-dichloro-3-nitroquinoline of Formula XVIII is reacted with *tert*-butyl carbazate or an alternate carbazate to provide a carbazate compound of Formula XIX. The reaction can be carried out by adding *tert*-butyl carbazate or an alternate carbazate to a solution of a 2,4-dichloro-3-nitroquinoline of Formula XVIII in a suitable solvent such as anhydrous dichloromethane in the presence of a base such as triethylamine. The reaction can be run at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods. Many quinolines of Formula XVIII are known or can be prepared using known synthetic methods (see for example, Andre et al., U.S. Patent No. 4,988,815 and references cited therein).

In step (2) of Reaction Scheme IV, a carbazate compound of Formula XIX is reduced to provide a 2-chloroquinolin-3-amine of Formula XX using the method of step (2) in Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (3) of Reaction Scheme IV, a 2-chloroquinolin-3-amine of Formula XX is reacted with an acyl halide of formula $R_2C(O)Cl$ or $R_2C(O)Br$, or a carboxylic acid or

equivalent thereof, using the methods of step (3) in Reaction Scheme I to provide a 4-chloro-1*H*-imidazo[4,5-*c*]quinoline of Formula XXI. The carboxylic acid or equivalent is selected such that it provides the desired R_2 substituent in compounds of Formula XXI. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (4) of Reaction Scheme IV, the *tert*-butoxycarbonyl or alternate oxyearbonyl group is removed from a 4-chloro-1*H*-imidazo[4,5-*c*]quinoline of Formula XXI using the method of step (4) of Reaction Scheme I to provide a 4-chloro-1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula XXII or a salt thereof. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (5a) of Reaction Scheme IV, a 4-chloro-1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula XXII or a salt thereof is treated with a ketone, aldehyde, or corresponding ketal or acetal using the method of step (5a) of Reaction Scheme I to provide a compound of Formula XXIII. The ketone, aldehyde, or corresponding ketal or acetal thereof, is selected with R_i and R_{ii} groups that will provide the desired R_1 substituent in a 4-chloro-1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula XXIVa. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

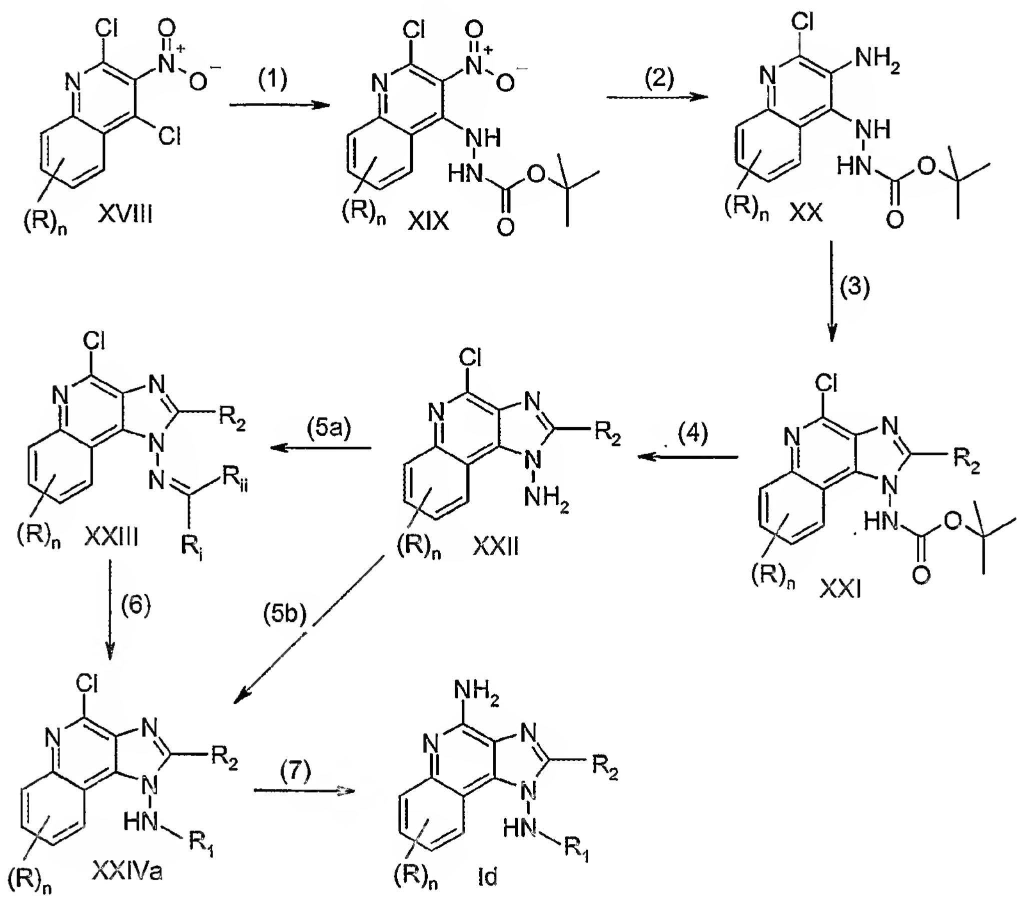
In step (6) of Reaction Scheme IV, a compound of Formula XXIII is reduced using the method of step (6) in Reaction Scheme I to provide a 4-chloro-1*H*-imidazo[4,5-*c*]quinolin-1-amine eompound of Formula XXIVa. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Alternatively, in step (5b) of Reaction Scheme IV, a 4-chloro-1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula XXII can be treated with a ketone and a borohydride using the method of step (5b) in Reaction Scheme I to provide a 4-chloro-1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula XXIVa. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (7) of Reaction Scheme IV, a 4-chloro-1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula XXIVa is aminated to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula Id, which is a subgenus of compounds of the Formulas I, I-1, I-2, and I-3. The reaction is carried out by heating (e.g., 125-175°C) a compound of Formula XXIVa under pressure in a sealed reactor in the presence of a solution of ammonia in an alkanol. The

product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme IV



Compounds of the invention can be prepared according to Reaction Scheme V wherein R, R_1, R_2 and n are as defined above.

In step (1) of Reaction Scheme V, a 4-chloro-1*H*-imidazo[4,5-*c*]quinoline of Formula XXI is aminated, using the method of step (7) in Reaction Scheme IV, to provide a 4-amino compound of the Formula XII. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (2) of Reaction Scheme V, the *tert*-butoxycarbonyl or alternate oxycarbonyl group is removed from a 4-amino compound of the Formula XII using the method of step (4) of Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of

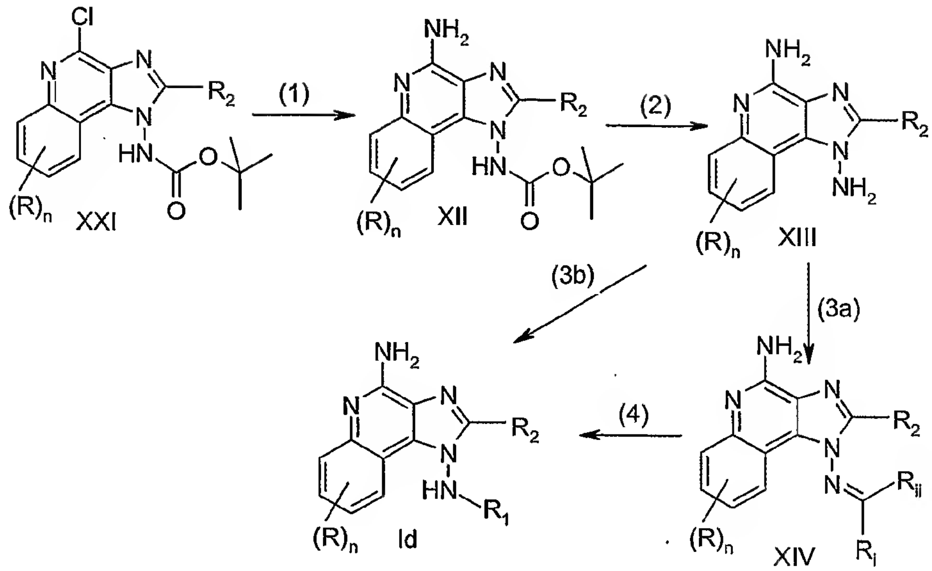
Formula XIII or a salt thereof. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (3a) of Reaction Scheme V, a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula XIII or a salt thereof is treated with a ketone, aldehyde, or corresponding ketal or acetal using the method of step (5a) of Reaction Scheme I to provide a compound of Formula XIV. The ketone, aldehyde, or corresponding ketal or acetal thereof, is selected with R_i and R_{ii} groups that will provide the desired R_1 substituent in a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine compound of Formula Id. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (4) of Reaction Scheme V, a compound of Formula XIV is reduced using the method of step (6) in Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine compound of Formula Id, which is a subgenus of compounds of the Formulas I, I-1, I-2, and I-3. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Alternatively, in step (3b) of Reaction Scheme V, a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula XIII or a salt thereof can be treated with a ketone and a borohydride using the method of step (5b) in Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine compound of Formula Id. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme V



Compounds of the invention can also be prepared according to Reaction Scheme VI wherein R, R_1', R_1, R_2 and n are as defined above.

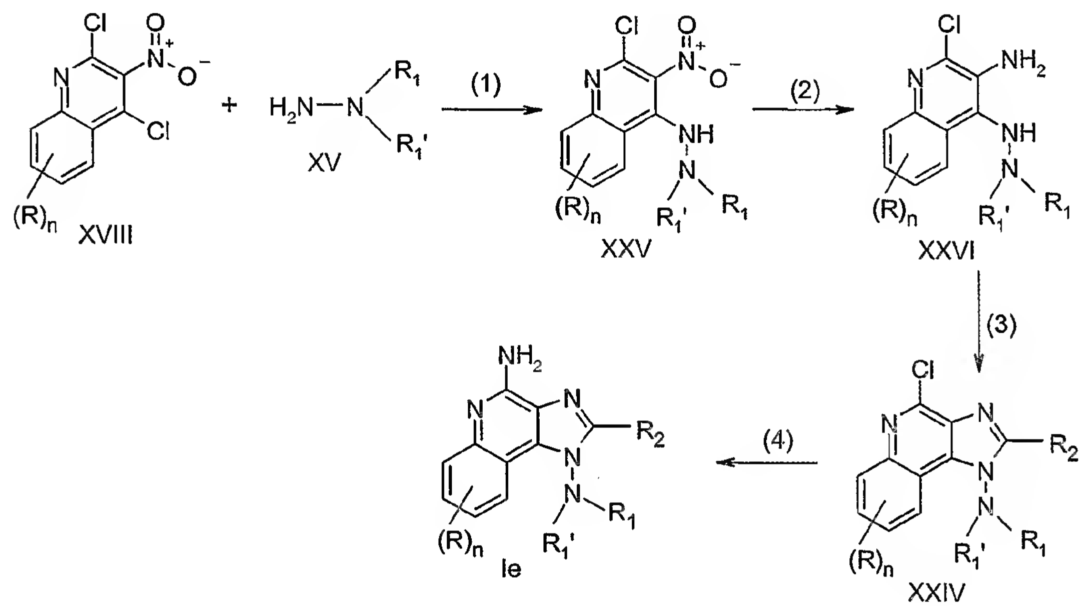
In step (1) of Reaction Scheme VI, a 2,4-dichloro-3-nitroquinoline of Formula XVIII is reacted with a hydrazino compound of Formula XV, using the method of step (1) in Reaction Scheme III, to provide a compound of Formula XXV. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (2) of Reaction Scheme VI, a compound of Formula XXV is reduced using the method of step (2) in Reaction Scheme I to provide a compound of Formula XXVI. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (3) of Reaction Scheme VI, a compound of Formula XXVI is reacted with an acyl halide of formula $R_2C(O)Cl$ or $R_2C(O)Br$, or a carboxylic acid or equivalent thereof using the methods of step (3) in Reaction Scheme I to provide a 4-chloro-1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula XXIV. The carboxylic acid or equivalent is selected such that it provides the desired R_2 substituent in a compound of Formula XXIV. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (4) of Reaction Scheme VI, a 4-chloro-1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula XXIV is aminated using the method of step (7) in Reaction Scheme IV to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula Ie, which is a subgenus of compounds of the Formulas I, I-1, I-2, and I-3. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme VI



Compounds of the invention can be prepared according to Reaction Scheme VII wherein R, R_1', R_{2a}, R_4, n, and Y are as defined above, and X_a is C_{1-20} alkylene.

In step (1) of Reaction Scheme VII, a 1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula VIIa or a salt thereof is treated with a ketal or acetal, containing a protected amino group, using the method of step (5a) of Reaction Scheme I to provide a compound of Formula XXVII. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

The amino ketal or acetal is selected with R_1' and X groups that will provide the desired R_1' and X groups in a 1*H*-imidazo[4,5-*c*]quinolin-1,4-diamine of Formula XXX, XXXI, or XXXII, which are subgenera of compounds of the Formulas I, I-1, I-2, and I-3. For example, *tert*-butyl (3,3-diethoxypropyl)carbamate will provide a compound where R_1' is hydrogen and X is ethylene. The amino group of an amino ketal or acetal can be

protected with a *tert*-butoxycarbonyl or an alternate oxycarbonyl group. For example, 1-amino-3,3-diethoxypropane can be reacted with di-*tert*-butyl dicarbonate in a suitable solvent such as tetrahydrofuran (THF) in the presence of triethylamine to provide *tert*-butyl (3,3-diethoxypropyl)carbamate.

In step (2) of Reaction Scheme VII, a compound of Formula XXVII is reduced using the method of step (6) in Reaction Scheme I to provide a compound of Formula XXVIII, which is a subgenus of compounds of the Formula IX. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (3) of Reaction Scheme VII, a compound of Formula XXVIII is oxidized to provide an *N*-oxide of Formula XXIX using the method of step (7) in Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (4) of Reaction Scheme VII, an N-oxide of Formula XXIX is aminated using the method of step (8) in Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula XXX, which is a subgenus of compounds of the Formulas I, I-1, I-2, and I-3. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

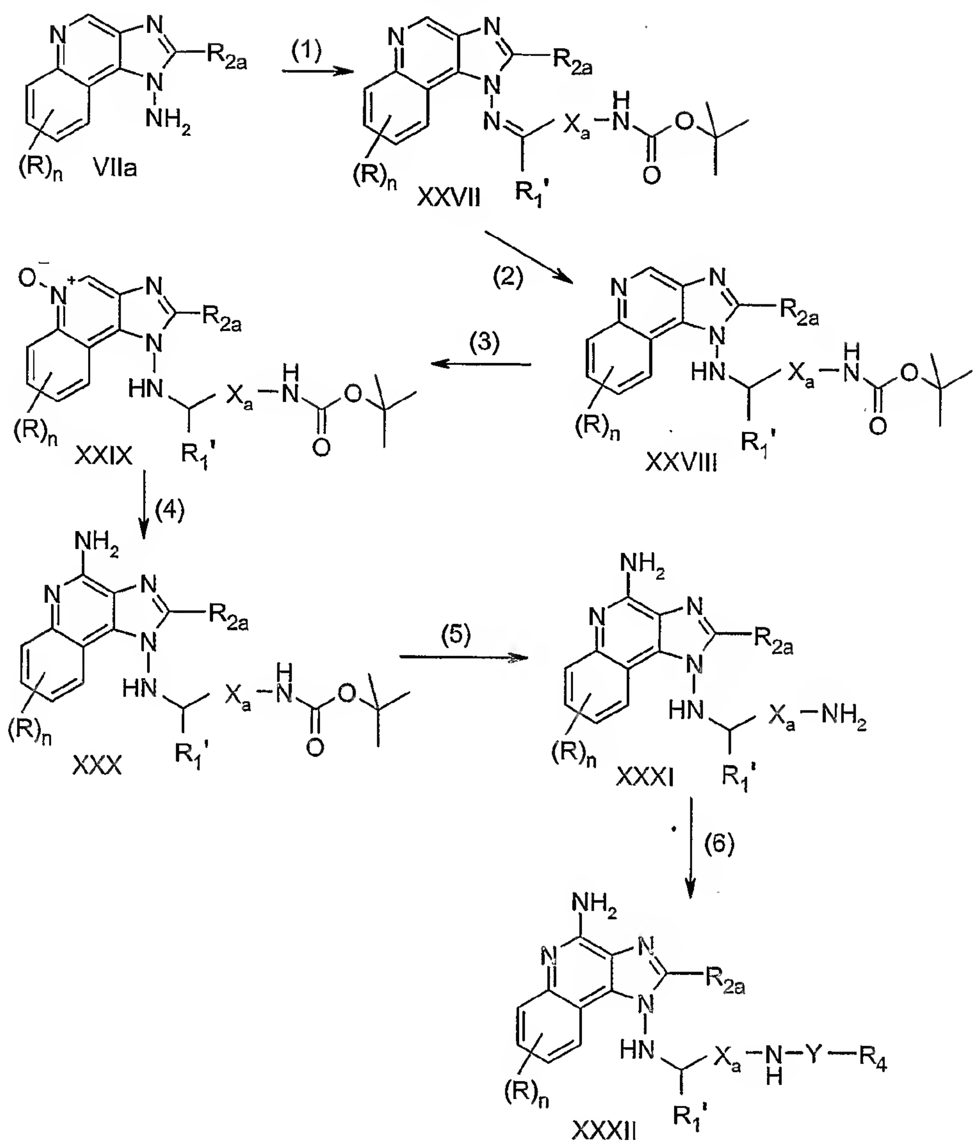
In step (5) of Reaction Scheme VII, a the *tert*-butoxycarbonyl or alternate oxycarbonyl group is removed from a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula XXX using the method of step (4) of Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula XXXI, which is a subgenus of compounds of the Formulas I, I-1, I-2, and I-3. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (6) of Reaction Scheme VII, a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula XXXI is converted to a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula XXXII using conventional methods. For example, a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula XXXI can react with an acid chloride of Formula $R_4C(O)Cl$ to provide a compound of Formula XXXII in which Y is -C(O)-. In addition, a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula XXXI can react with sulfonyl chloride of Formula $R_4S(O)_2Cl$ or a sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to provide a compound of Formula XXXII in which Y is $-S(O)_2-$. Numerous acid chlorides of Formula $R_4C(O)Cl$, sulfonyl chlorides of Formula $R_4S(O)_2Cl$, and sulfonic anhydrides of

Formula $(R_4S(O)_2)_2O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the acid chloride of Formula $R_4C(O)Cl$, sulfonyl chloride of Formula $R_4S(O)_2Cl$, or sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to a cooled solution of a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula XXXI and a base such as triethylamine in a suitable solvent such as chloroform, dichloromethane, or acetonitrile. The reaction can be carried out at ambient temperature or at a sub-ambient temperature such as 0 °C. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Ureas of Formula XXXII, where Y is $-C(R_7)-N(R_9)-$, in which R_7 is =O, and R_9 is as defined above, can be prepared by reacting a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula XXXI with isocyanates of Formula $R_4N{=}C{=}O$. Numerous isocyanates of Formula $R_4N{=}C{=}O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the isocyanate of Formula $R_4N{=}C{=}O$ to a cooled solution of a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of the Formula XXXI in a suitable solvent such as dichloromethane or chloroform. The reaction can be carried out at ambient temperature or at a sub-ambient temperature such as 0 °C. Alternatively, a compound of Formula XXXI can be treated with a thioisocyanate of Formula $R_4N{=}C{=}S$, or a carbamoyl chloride of Formula $R_4N(R_9)-C(O)Cl$ to provide a compound of Formula XXXII, where Y is $-C(S)-N(R_9)-$, in which R_9, is as defined above. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

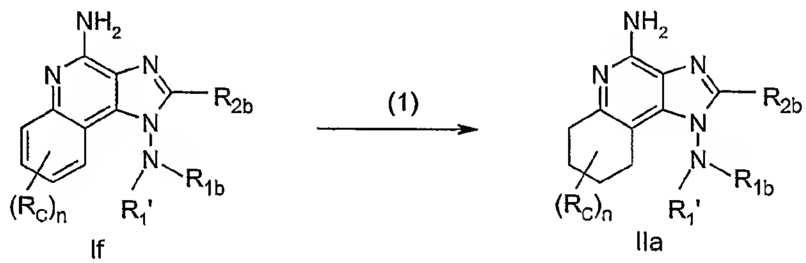
Reaction Scheme VII



Compounds of the invention can be prepared according to Reaction Scheme VIII where n is as defined above; each R_C is independently selected from the group consisting of hydroxy, alkyl, and alkoxy; and R_{1b} and R_{2b} are a subset of R_1 and R_2, respectively, as defined above, which do not include those groups that one skilled in the art would recognize as being susceptible to reduction under the acidic hydrogenation conditions in step (1). These susceptible groups include, for example, alkenyl, alkynyl, and aryl groups, and groups bearing nitro substituents.

In step (1) of Reaction Scheme VIII, a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula If is reduced to provide a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula IIa, which is a subgenus of compounds of the Formulas II and II-1. The reaction can be conveniently carried out by suspending or dissolving a compound of Formula If in trifluoroacetic acid, adding platinum(IV) oxide, and hydrogenating under an atmosphere of hydrogen. The reaction can be carried out in a Parr apparatus. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme VIII



Compounds of the invention may be prepared according to Reaction Scheme IX where R_A, R_1, R_1', R_2, and n is as defined above; and each R_a is independently alkyl. Steps (1) through (4) may be carried out as described in U.S. Patent No. 5,352,784 and documents cited therein. In step (1) the amino group of a compound of Formula XXXIII may be acylated to provide a compound of Formula XXXIV. The reaction may be conveniently carried out by reacting a compound of Formula XXXIII with an alkyl malonyl chloride in the presence of a base such as triethylamine in a suitable solvent such as methylene chloride. The product or a pharmaceutically acceptable salt thereof may be isolated using conventional methods. Certain compounds of Formula XXXIII are commercially available and others can be prepared as described in U.S. Patent No. 5,352,784 and documents cited therein. Alkyl malonyl chlorides are known, some of which are commercially available, and others can be made my known methods.

In step (2) of Reaction Scheme IX, a compound of Formula XXXIV may be cyclized to provide a compound of Formula XXXV. The reaction may be conveniently carried out by adding a solution of a compound of Formula XXXIV in a suitable solvent such as THF to a suspension of sodium hydride (or other base capable of removing a malonyl methylene proton) in a suitable solvent such as THF. The reaction may be run at

an elevated temperature, for example the reflux temperature. The product or a pharmaceutically acceptable salt thereof may be isolated using conventional methods.

In step (3) of Reaction Scheme IX, a compound of Formula XXXV may be hydrolyzed and decarboxylated to provide a compound of Formula XXXVI. The reaction may be carried out by conventional methods, for example, by combining a compound of Formula XXXV with an acid, such as hydrochloric acid, with heating. The product may be isolated using conventional methods.

In step (4) of Reaction Scheme IX, a compound of Formula XXXVI may be nitrated to provide a compound of Formula XXXVII. The reaction may be carried out under conventional nitration conditions, such as by heating a compound of Formula XXXVI in the presence of nitric acid, preferably in a solvent such acetic acid. The product or a pharmaceutically acceptable salt thereof may be isolated using conventional methods.

In step (5) of Reaction Scheme IX, a compound of Formula XXXVII may be chlorinated to provide a 2,4-dichloro-3-nitro-5,6,7,8-tetrahydroquinoline of Formula XXXVIII. The reaction may be carried out by combining a compound of Formula XXXVII with a conventional chlorinating agent (e.g., phosphorus oxychloride, thionyl chloride, phosgene, oxalyl chloride, or phosphorus pentachloride), optionally in solvent such as *N,N*-dimethylformamide (DMF) or methylene chloride, with heating (e.g., at the reflux temperature). The product or a pharmaceutically acceptable salt thereof may be isolated from the reaction mixture using conventional methods.

In step (6) of Reaction Scheme IX, a 2,4-dichloro-3-nitro-5,6,7,8-tetrahydroquinoline of Formula XXXVIII may be reacted with a hydrazino compound of Formula XV ($H_2N\text{-}N(R_1')(R_1)$), using the method of step (1) in Reaction Scheme III, to provide a compound of Formula XXXIX. The product or a pharmaceutically acceptable salt thereof may be isolated by conventional methods.

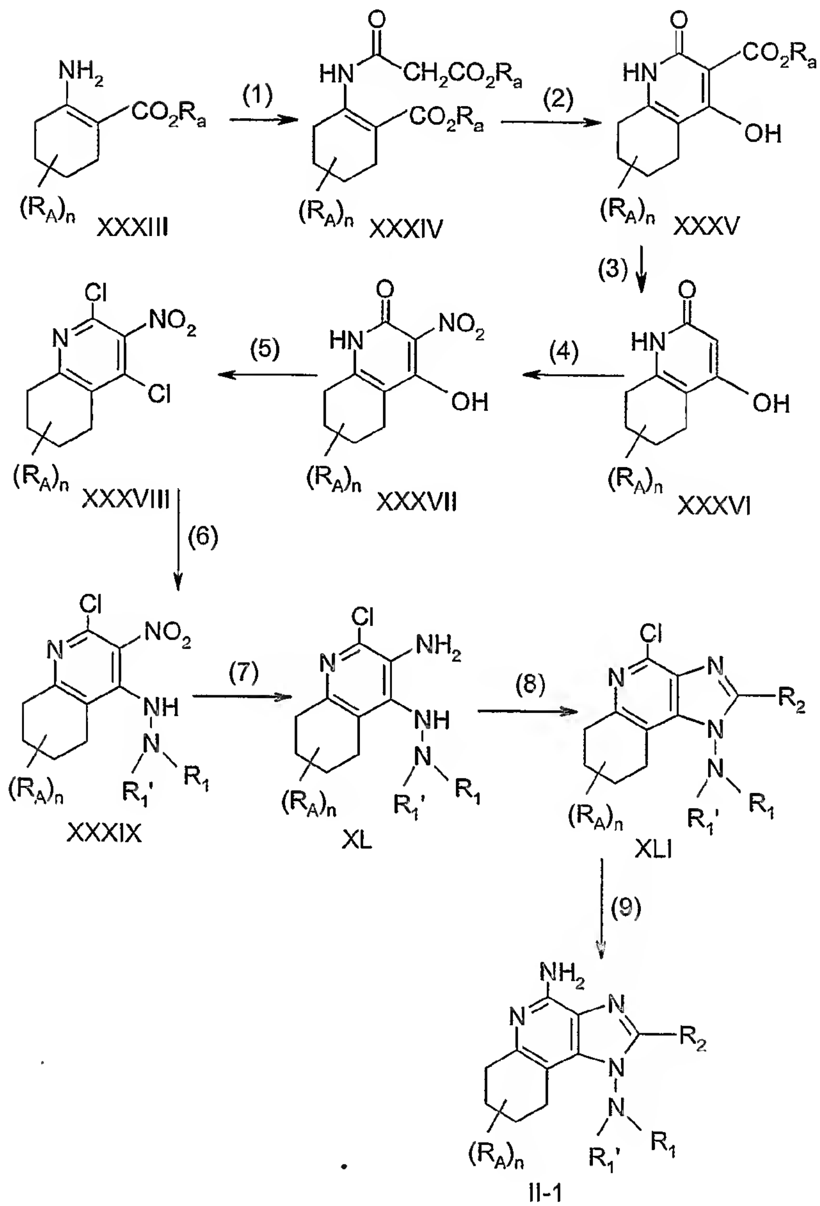
In step (7) of Reaction Scheme IX, a compound of Formula XXXIX may be reduced using the method of step (2) in Reaction Scheme I to provide a compound of Formula XL. The product or a pharmaceutically acceptable salt thereof may be isolated by conventional methods.

In step (8) of Reaction Scheme IX, a compound of Formula XL may be reacted with an acyl halide of formula $R_2C(O)Cl$ or $R_2C(O)Br$, or a carboxylic acid or equivalent

thereof using the methods of step (3) in Reaction Scheme I to provide a 4-chloro-1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula XLI. The carboxylic acid or equivalent may be selected such that it provides the desired R_2 substituent in a compound of Formula II-1. The product or a pharmaceutically acceptable salt thereof may be isolated by conventional methods.

In step (9) of Reaction Scheme IX, a 4-chloro-1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula XLI may be aminated using the method of step (7) in Reaction Scheme IV to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula II-1. The product or a pharmaceutically acceptable salt thereof may be isolated by conventional methods.

Reaction Scheme IX



For some embodiments, compounds of the invention are prepared according to Reaction Scheme X, wherein R, R_{1a}, R_{2a}, and l are as defined above; Hal is ehloro, bromo, or iodo; R_{3a} is -Z'-R_4', -Z'-X'-R_4', -Z'-X'-Y'-R_4', or -Z'-X'-R_5'; wherein R_4', Y', X', and R_5' are as defined above; and Z' is a bond.

In step (1) of Reaction Scheme X, a 4-chloro-3-nitroquinoline of Formula XLIV is converted to a carbazate of Formula XLV according to the method described in step (1) of

Reaction Scheme I. Compounds of Formula XLIV ean be readily prepared using known synthetic routes; see for example, U.S. Patent Nos. 4,689,338 (Gerster), 5,367,076 (Gerster), 6,331,539 (Crooks et al.), 6,451,810 (Coleman et al.), 6,541,485 (Crooks et al.) and the documents cited therein.

In steps (2) and (3) of Reaction Scheme X, a nitro-substituted quinoline of Formula XLV is first reduced to an amino-substituted quinoline of Formula XLVI, which is then cyclized to a 1*H*-imidazoquinoline of Formula XLVII. Steps (2) and (3) of Reaction Scheme X can be carried out as described for steps (2) and (3) of Reaction Scheme I.

In step (4) of Reaction Scheme X, the *tert*-butoxycarbonyl group of a 1*H*-imidazoquinoline of Formula XLVII is hydrolyzed under acidic conditions to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula VIIb or a pharmaceutically acceptable salt thereof. The reaction is conveniently carried out as described in step (4) of Reaction Scheme I.

The 1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula VIIb is then converted to a 1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula IXc using either a two-step procedure as shown in steps (5a) and (6) of Reaction Scheme X or a one-step procedure as shown in step (5b). The two-step procedure, in which a compound of Formula VIIIb is isolated, can be carried out as described in steps (5a) and (6) of Reaction Scheme I. In step (5a), the ketone, aldehyde, or corresponding ketal or acetal thereof, is selected with R_i and R_{ii} groups that will provide the desired R_{1a} substituent in a 1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula IXc. Step (5b) of Reaction Scheme X can be carried out as described for step (5b) of Reaction Scheme I.

In steps (7) and (8) of Reaction Scheme X, a 1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula IXc is first oxidized to an *N*-oxide of Formula Xb, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula Ig, which is a subgenus of the compounds of the Formulas I, I-1, I-2, and I-3. Steps (7) and (8) of Reaction Scheme X can be carried out according to the procedures described in steps (7) and (8) of Reaction Scheme I.

Step (9) of Reaction Scheme X can be carried out using known palladium-catalyzed coupling reactions such as Suzuki coupling, Stille coupling, Sonogashira coupling, and the Heck reaction. For example, a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula Ig undergoes Suzuki coupling with a boronic acid of Formula R_{3a}-$B(OH)_2$, an

anhydride thereof, or a boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$ to provide an 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula I-1b, a subgenus of Formulas I and I-1, wherein R_{3a} is -Z'-R_4',

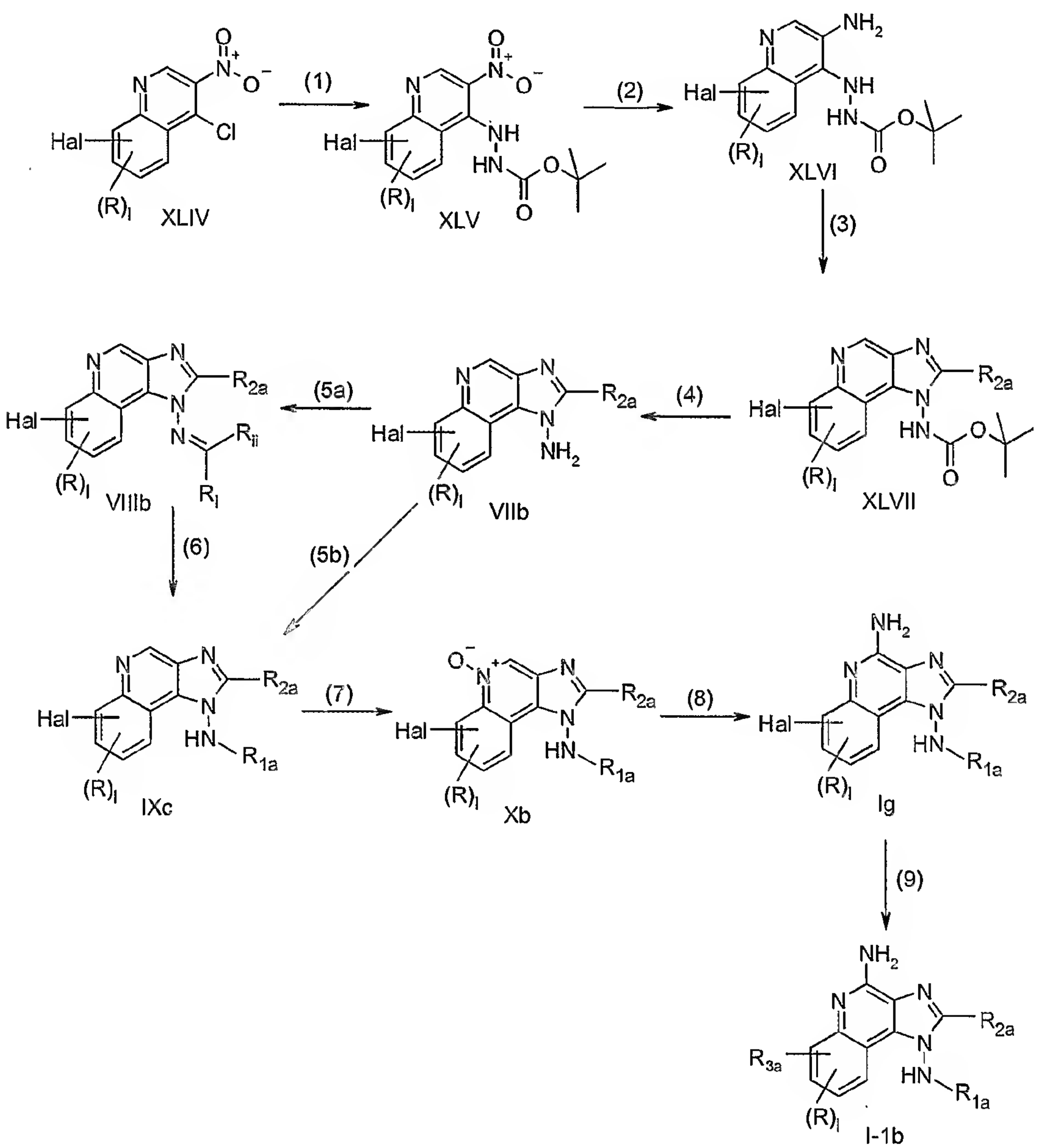
-Z'-X'-R_4', -Z'-X'-Y'-R_4', or -Z'-X'-R_5'; -Z' is a bond; -X'- is alkenylene, arylene, or heteroarylene optionally terminated by arylene or heteroarylene; and R_4', Y', and R_5' are as defined above. The coupling is carried out by combining a compound of Formula Ig with a boronie acid or an ester or anhydride thereof in the presence of palladium (II) acetate, triphenylphosphine, and a base such as sodium carbonate in a suitable solvent such as *n*-propanol. The reaction can be carried out at an elevated temperature (e.g., 80-100°C). Numerous boronic acids of Formula R_{3a}-B(OH)$_2$, anhydrides thereof, and boronic acid esters of Formula R_{3a}-B(O-alkyl)$_2$ are commercially available; others can be readily prepared using known synthetic methods. See, for example, Li, W. et al, *J. Org. Chem.*, *67*, 5394-5397 (2002). The product of Formula I-1b or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

The Heck reaction can also be used in step (9) of Reaction Scheme X to provide compounds of Formula I-1b, wherein R_{3a} is -Z'-X'-R_4' or -Z'-X'-Y'-R_4'; -Z' is a bond; -X'- is alkenylene optionally terminated by arylene or heteroarylene; and R_4' and Y' are as defined above. The Heck reaction is carried out by coupling a 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula Ig with a vinyl-substituted arylene or heteroarylene compound. Several vinyl-substituted arylene or heteroarylene compounds, such as 2-vinylpyridine, 3-vinylpyridine, and 4-vinylpyridine, are commercially available; others can be prepared by known methods. The reaction is conveniently carried out by combining the 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula Ig and the vinyl-substituted compound in the presence of palladium (II) acetate, triphenylphosphine or tri-*ortho*-tolylphosphine, and a base such as triethylamine in a suitable solvent such as acetonitrile or toluene. The reaction can be carried out at an elevated temperature such as 100-120 °C under an inert atmosphere. The compound or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Compounds of Formula I-1b, wherein R_{3a} is -Z'-X'-R_4' or -Z'-X'-Y'-R_4', -Z' is a bond and -X'- is alkenylene optionally terminated by arylene or heteroarylene, may be reduced to provide compounds wherein -X'- is alkylene optionally terminated by arylene or heteroarylene. For example, compounds wherein R_{3a} is a 2-(pyridin-3-yl)ethyl group

may be prepared in this manner. The reduction can be carried out by hydrogenation using a conventional heterogeneous hydrogenation catalyst such as palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as ethanol, methanol, or mixtures thereof. The compound or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme X



For some embodiments, compounds of the invention can be prepared according to Reaction Scheme XI where R, R_{1a}, R_{2a}, and l are as defined above; Boc is *tert*-butoxycarbonyl; R_{3b} is -Z'-R_4', -Z'-X'-R_4', -Z'-X'-Y'-R_4', or -Z'-X'-R_5'; X', Y', and R_4' are as defined above; and Z' is -O-.

In step (1) of Reaction Scheme XI, a benzyloxyaniline of Formula XLVIII is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide an imine of Formula XLIX. The reaction is conveniently carried out by adding a solution of a benzyloxyaniline of Formula XLVIII to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature such as 45 °C. The product can be isolated using conventional methods.

In step (2) of Reaction Scheme XI, an imine of Formula XLIX undergoes thermolysis and cyclization to provide a benzyloxyquinolin-4-ol of Formula L. The reaction is conveniently carried out in a heat transfer fluid such as DOWTHERM A heat transfer fluid at a temperature between 200 and 250 °C. The product can be isolated using conventional methods.

In step (3) of Reaetion Scheme XI, a benzyloxyquinolin-4-ol of Formula L is nitrated under conventional nitration conditions to provide a benzyloxy-3-nitroquinolin-4-ol of Formula LI. The reaction is conveniently carried out by adding nitric acid to the benzyloxyquinolin-4-ol of Formula L in a suitable solvent such as propionic acid and heating the mixture at an elevated temperature such as 125 °C. The product can be isolated using conventional methods.

In step (4) of Reaction Scheme XI, a benzyloxy-3-nitroquinolin-4-ol of Formula LI is chlorinated using conventional chlorination chemistry to provide a benzyloxy-4-chloro-3-nitroquinoline of Formula LII. The reaction is conveniently carried out by treating the benzyloxy-3-nitroquinolin-4-ol of Formula LI with phosphorous oxychloride in a suitable solvent such as DMF. The reaction can be carried out at ambient temperature or at an elevated temperature such as 100 °C, and the product can be isolated using eonventional methods.

In step (5) of Reaction Scheme XI, a benzyloxy-4-chloro-3-nitroquinoline of Formula LII is converted to a carbazate of Formula LIII. The reaction is conveniently carried out as described in step (1) of Reaction Scheme I.

In steps (6) and (7) of Reaction Scheme XI, a nitro-substituted quinoline of Formula LIII is first reduced to an amino-substituted quinoline of Formula LIV, which is then cyclized to a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline of Formula LV. Steps (6) and (7) of Reaction Scheme XI can be carried out as described for steps (2) and (3) of Reaction Scheme I.

In step (8) of Reaction Scheme XI, the Boc group of a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline of Formula LV is hydrolyzed under acidic conditions to provide a benzyloxy-1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula XLIIa or a pharmaceutically acceptable salt thereof. The reaction is conveniently carried out as described in step (4) of Reaction Scheme I.

The benzyloxy-1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula XLIIa is then converted to a benzyloxy-1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula XLIIIa using either a two-step procedure as shown in steps (9a) and (10) of Reaction Scheme XI or a one-step procedure as shown in step (9b). The two-step procedure, in which a compound of Formula LVI is isolated, can be carried out as described in steps (5a) and (6) of Reaction Seheme I. In step (9a), the ketone, aldehyde, or corresponding ketal or acetal thereof, is seleeted with R_i and R_{ii} groups that will provide the desired R_{1a} substituent in a benzyloxy-1*H*-imidazo[4,5-*c*]quinolin-1-amine compound of Formula XLIIIa. Step (9b) of Reaction Scheme XI can be carried out as described for step (5b) of Reaction Scheme I.

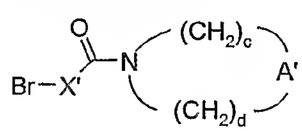
In steps (11) and (12) of Reaction Scheme XI, a benzyloxy-1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula XLIIIa is first oxidized to an *N*-oxide of Formula LVII, which is then aminated to provide a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula LVIII, which is a subgenus of the compounds of the Formulas I and I-1. Steps (11) and (12) of Reaction Scheme XI can be carried out according to the procedures described in steps (7) and (8) of Reaction Scheme I.

In step (13) of Reaction Scheme XI, the benzyl group of a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula LVIII is cleaved to provide a hydroxy-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula Ih. The cleavage is eonveniently carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium on carbon in a solvent such as ethanol. The product or pharmaeeutically acceptable salt thereof can be isolated using conventional methods.

In step (14) of Reaction Scheme XI a hydroxy-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula Ih is converted to an ether-substituted 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula I-1c (a subgenus of compounds of Formulas I and I-1) using a Williamson-type ether synthesis. The reaction is effected by treating a compound of Formula Ih with an alkyl halide of Formula Halide-R_4', Halide-X'-Y'-R_4', Halide-X'-R_4', or Halide-X'-R_5' in the presence of a base. The reaction is conveniently carried out by combining the alkyl halide with a compound of Formula Ih in a solvent such as DMF in the presence of a suitable base such as cesium carbonate. The reaction can be carried out at ambient temperature or at an elevated temperature, for example 65 °C or 85 °C. Alternatively, the reaction can be carried out by treating a solution of a compound of Formula Ih in a solvent such as DMF with sodium hydride and then adding the alkyl halide. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Numerous reagents of Formulas Halide-R_4', Halide-X'-R_4', and Halide-X'-Y'-R_4' are commercially available, for example, bromo-substituted ketones, esters, and heterocycles. Other reagents of Formulas Halide-R_4', Halide-X'-Y'-R_4', or Halide-X'-R_5' can be prepared using conventional synthetic methods; for example, a bromo-substituted acid halide of Formula ClC(O)-X'-Br can be treated with a secondary amine in a suitable solvent such as dichloromethane to provide a variety of bromo-substituted amides of Formula

Br-X'-C(O)-N(R_{11})-R_4' or



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The reaction can be run at a sub-ambient temperature such as -25 °C, and the product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

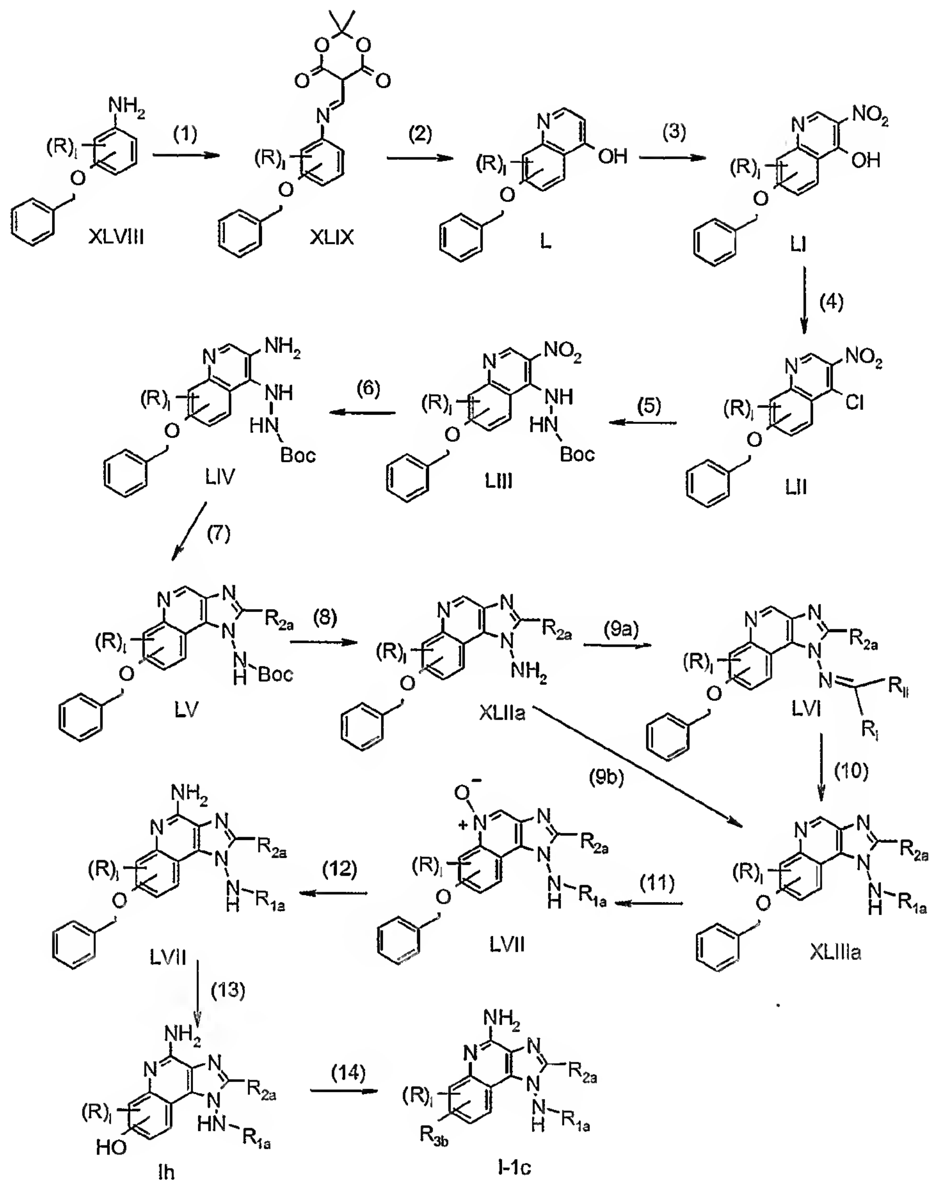
Reagents of Formula I-X'-NH-C(O)-O-C(CH_3)$_3$ can be prepared in two steps from amino alcohols of Formula HO-X'-NH_2, many of which are commercially available or readily prepared by known synthetic methods. An amino alcohol of Formula HO-X'-NH_2 is first protected with a *tert*-butoxy carbonyl group by treating the amino alcohol with di-*tert*-butyl dicarbonate in the presence of a base such as aqueous sodium hydroxide in a suitable solvent such as tetrahydrofuran. The resulting hydroxyalkylcarbamate of Formula

HO-X'-NH-C(O)-O-C(CH_3)$_3$ is then treated with a solution of iodine, triphenylphosphine, and imidazole at ambient temperature in a suitable solvent such as dichloromethane. The product of Formula I-X'-NH-C(O)-O-C(CH_3)$_3$ can be isolated using conventional methods.

Step (14) of Reaction Scheme XI can alternatively be carried out by treating a hydroxy-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula Ih with an alcohol of Formula HO-X'-Y'-R_4', HO-X'-R_5', HO-X'-R_4', or HO-R_4' under Mitsunobu reaction conditions. Numerous alcohols of these formulas are commercially available, and others can be prepared using conventional synthetic methods. The reaction is conveniently carried out by out by adding triphenylphosphine and an alcohol of Formula HO-X'-Y'-R_4', HO-X'-R_5', HO-X'-R_4', or HO-R_4' to a solution of a compound of Formula Ih in a suitable solvent such as tetrahydrofuran and then slowly adding diisopropyl azodicarboxylate or diethyl azodicarboxylate. The reaction can be carried out at ambient temperature or at a sub-ambient temperature, such as 0 °C. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Compounds of Formula I-1c, wherein R_{3b} is -O-X'-NH-C(O)-O-C(CH_3)$_3$, can be prepared by treating compounds of Formula Ih with alcohols such as *tert*-butyl *N*-(4-hydroxybutyl)carbamate and *tert*-butyl *N*-(5-hydroxypentyl)carbamate under Mitsunobu conditions or with alkyl halides of Formula I-X'-NH-C(O)-O-C(CH_3)$_3$ in a Williamson-type ether synthesis. These compounds of Formula I-1c, wherein R_{3b} is -O-X'-NH-C(O)-O-C(CH_3)$_3$, are then readily converted to other compounds of Formula I-1c using conventional synthetic methods. For example, compounds in which R_{3b} is -O-X'-NH-C(O)-O-C(CH_3)$_3$ can be deprotected and treated according to the methods described in steps (5) and (6) of Reaction Scheme VII, Parts F and G of Example 14, and Examples 15 and 23 to provide compounds of Formula I-1c wherein R_{3b} is -Z'-X'-Y'-R_4'; Z' is -O-; Y' is -NH-Q-; Q is -C(R_7)-, -S(O)$_2$-, or -C(R_7)-N(R_{11})-; and X', R_4', R_7, and R_{11} are as defined above. Compounds in which R_{3b} is a 2-methanesulfonylaminoethoxy group or a 3-methanesulfonylaminopropoxy group are available using these methods.

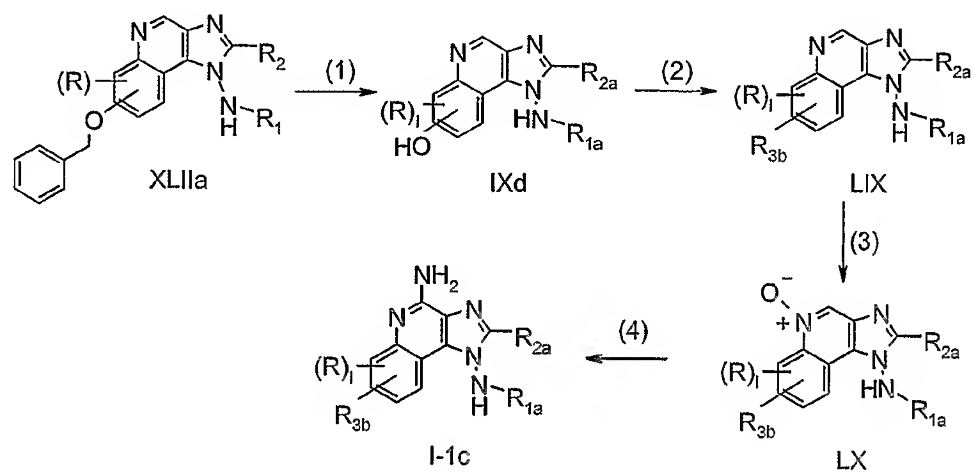
Reaction Scheme XI



For some embodiments, compounds of Formula I-1c can be prepared according to Reaction Scheme XII, in which R, R_{1a}, R_{2a}, R_{3b}, and l are as defined above. In step (1) of Reaction Scheme XII, the benzyl group of a benzyloxy-1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula XLIIa is cleaved to provide a hydroxy-1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula IXd. In step (2) of Reaction Scheme XII a hydroxy-1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula IXd is converted to an ether-substituted 1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula LIX. In steps (3) and (4) of Reaction Scheme XII, an

ether-substituted 1*H*-imidazo[4,5-*c*]quinolin-1-amine of Formula LIX is first oxidized to an *N*-oxide of Formula LX, which is then aminated to provide an ether-substituted 1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine of Formula I-1c, which is a subgenus of the compounds of Formula I-1. Steps (1), (2), (3), and (4) of Reaction Scheme XII can be carried out as described in steps (13), (14), (11), and (12), respectively, of Reaction Scheme XI.

Reaction Scheme XII



Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound of the invention as described above in combination with a pharmaceutically acceptable carrier.

The term “a therapeutically effective amount” or "effective amount" means an amount of the compound sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 ng/kg to about 50 mg/kg,

preferably about 10 μg/kg to about 5 mg/kg, of the compound to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds of the invention have been shown to modulate (e.g., induce) the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of eompounds aceording to the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. The animal to which the compound or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound may provide therapeutic treatment. Alternatively, the compound may be administered to the animal prior to the animal acquiring the disease so that administration of the compound may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds of the invention may affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction.

Certain compounds may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, certain compounds may cause proliferation and differentiation of B-lymphocytes.

Compounds of the invention also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ is induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 are inhibited upon administration of certain compounds.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which IRMs identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection; and

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, renal cell carcinoma, leukemias including but not limited to myelogeous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers; and

(e) T_H2-mediated, atopic, and autoimmune diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, Ommen's syndrome, discoid lupus, alopecia areata, inhibition of keloid formation and other types of scarring, and enhancing would healing, including chronic wounds.

IRMs identified herein also may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens, toxoids, toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; recombinant proteins; glycoproteins; peptides; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

IRMs may also be particularly helpful in individuals having compromised immune function. For example, IRM compounds may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of Formula I, I-1, I-2, I-3, II, or II-1 to the animal.

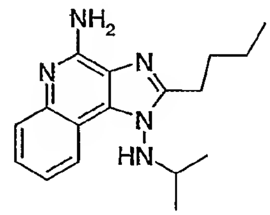
An amount of a compound effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased over the background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

Example 1

2-Butyl-N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 4-chloro-3-nitroquinoline (5.00 g, 24.0 mmol) in 120 mL of anhydrous CH_2Cl_2 was treated with triethylamine (6.7 mL, 48.2 mmol) and *tert*-butyl carbazate (3.20 g, 24.2 mmol). After stirring under nitrogen for 2.5 hour (h), an additional portion of *tert*-butyl carbazate (3.2 g, 24.2 mmol) was added. After stirring overnight, the deep red solution was washed with H_2O (2X) and brine. The organic portion was dried over Na_2SO_4 and concentrated to give a red foam. The material was passed through a SiO_2 column eluting with 2.5% methanol/CH_2Cl_2. The resulting red powder was treated with 5:1 hexanes/CH_2Cl_2 and filtered. The solid was washed several times with hexanes and was dried under vacuum to give *tert*-butyl *N'*-(3-nitroquinolin-4-yl)hydrazinecarboxylate (4.97 g) as an orange powder.

Part B

A suspension of *tert*-butyl *N'*-(3-nitroquinolin-4-yl)hydrazinecarboxylate (2.50 g, 8.22 mmol) in 150 mL of isopropanol was treated with 1.0 g of 10% palladium on carbon and the mixture was shaken under an atmosphere of hydrogen (3.8×10^5 Pa) for 2 h. The reaction mixture was then filtered through a pad of CELITE filter agent and rinsed with isopropanol, and the filtrate was concentrated under reduced pressure to give *N'*-(3-aminoquinolin-4-yl)hydrazine *tert*-butyl carboxylate (2.18 g) as a yellow solid.

Part C

A solution of *N'*-(3-aminoquinolin-4-yl)hydrazine *tert*-butyl carboxylate (2.18 g, 7.96 mmol) in 80 mL of anhydrous CH_2Cl_2 was cooled to 0 °C and treated with triethylamine (1.12 mL, 8.00 mmol) and valeryl chloride (0.95 mL, 8.00 mmol) under an

atmosphere of nitrogen. After stirring for 3 h, the reaction mixture was concentrated under reduced pressure and the residue was treated with Et_2O and filtered. The filtrate was concentrated and the resulting black tar was dissolved in 80 mL of ethanol and treated with 3 mL of triethylamine and the mixture was refluxed overnight. The reaction mixture was concentrated under reduced pressure. Chromatography (SiO_2, 1-5% methanol (MeOH)/$CHCl_3$) gave *tert*-butyl *N*-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate (1.41 g) as a mauve foam.

Part D

tert-Butyl *N*-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate (830 mg, 2.44 mmol) was dissolved in 20 mL of 1.5 M HCl in ethanol (EtOH) and the reaction mixture was heated to reflux for 1.5 h. The reaction mixture was cooled and concentrated under reduced pressure to give a brown solid. The material was dissolved in 50 mL of hot isopropanol and the solution was allowed to cool overnight. The resulting crystals were isolated by filtration. A second crop was obtained from the filtrate by crystallization from isopropanol/Et_2O. The total yield of 2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine hydrochloride was 570 mg. mp > 250 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 9.68 (s, 1H), 9.35 (d, J = 8.3 Hz, 1H), 8.47 (d, J = 8.0 Hz, 1H), 8.03 (t, J = 7.1 Hz, 1H), 7.98 (t, J = 7.1 Hz, 1H), 6.85 (s, 2H), 3.13 (t, J = 7.6 Hz, 2H), 1.89, (m, 2H), 1.49 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.5, 139.4, 136.1, 134.0, 131.8, 130.4, 128.9, 122.6, 120.2, 115.6, 28.2, 25.7, 22.1, 13.3; Anal. Calcd for $C_{14}H_{16}N_4 \cdot HCl$: C, 60.76; H, 6.19; N, 20.24; Cl, 12.81. Found: C, 60.78; H, 6.19; N, 20.21; Cl, 12.78.

Part E

A solution of 2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine hydrochloride (520 mg, 2.17 mmol) in 10 mL of isopropanol was treated with 2 mL of acetone and 200 mg of DOWEX W50-X1 acid resin. The reaction mixture was heated to 55 °C overnight. The reaction mixture was treated with an additional 10 mL of isopropanol and 5 mL of acetone and heated to 70 °C for 2 h. The reaction mixture was filtered and the filtrate was treated with 0.5 mL of triethylamine and concentrated under reduced pressure. Chromatography (SiO_2, 3% MeOH/$CHCl_3$) gave *N*-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine (421 mg) as a brown oil.

Part F

A solution of *N*-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine (406 mg, 1.45 mmol) in 15 mL of MeOH was treated with $NaBH_4$ (500 mg, 13.2 mmol). After stirring for 2 days (d), the reaction was quenched with saturated $NaHCO_3$ solution and extracted into ethyl acetate (EtOAc). The organic portion was washed with H_2O and brine and dried over Na_2SO_4. Chromatography (SiO_2, EtOAc) gave *N*-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (372 mg) as a mauve solid.

Part G

A solution of *N*-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (334 mg, 1.18 mmol) in 10 mL of CH_2Cl_2 was treated with 3-chloroperoxybenzoic acid (MCPBA) (77% max., 334 mg, 1.45 mmol). After stirring for 3 h, the reaction was quenched with saturated $NaHCO_3$ solution and extracted into CH_2Cl_2. The organic portion was washed with saturated $NaHCO_3$ solution, H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated to give *N*-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (338 mg) as a light brown solid.

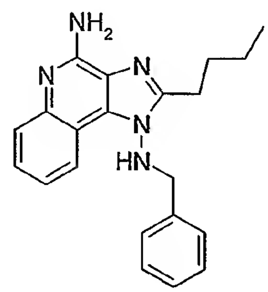
Part H

A solution of *N*-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (332 mg, 1.11 mmol) in 15 mL of 1,2-dichloroethane was placed in a pressure vessel and heated to 70 °C. The rapidly stirred solution was then treated with 3 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (233 mg, 1.22 mmol), the reaction vessel was capped, and heating was continued for 2 h. The reaction mixture was then cooled to ambient temperature and treated with 50 mL of CH_2Cl_2. The reaction mixture was washed with H_2O, 1% Na_2CO_3 solution (3X), H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated. Chromatography (SiO_2, 5-10% MeOH/$CHCl_3$) gave 320 mg of a light brown solid. Crystallization from CH_2Cl_2/hexanes gave 2-butyl-N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (230 mg) as colorless crystals. mp 157.1-158.7 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 8.40 (m, 1H), 7.80 (m, 1H), 7.50 (m, 1H), 7.31 (m, 1H), 5.41 (s, 2H), 4.95 (s, 1H), 3.68 (m, 1H), 2.96 (t, J = 7.6 Hz, 2H), 1.93-1.82 (m, 2H), 1.48 (m, 2H), 1.16 d, J = 6.4 Hz, 6H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75

MHz, DMSO-d_6) δ 155.1, 151.8, 144.7, 133.1, 127.3, 126.6, 124.7, 122.0, 120.4, 115.3, 52.1, 30.3, 26.8, 23.0, 20.8, 14.2; MS m/z 298 $(M + H)^+$; Anal. Calcd for $C_{17}H_{23}N_5$: C, 68.66; H, 7.80; N, 23.55. Found: C, 68.30; H, 7.68; N, 23.33.

Example 2

N[1]-Benzyl-2-butyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine hydrochloride (503 mg, 1.82 mmol) in 10 mL of isopropanol was treated with benzaldehyde (220 µL, 2.17 mmol) and 200 mg of DOWEX W50-X1 acid resin. The reaction mixture was heated to reflux overnight. The reaction mixture was filtered, and the filtrate was treated with 0.5 mL of triethylamine and concentrated under reduced pressure. The resulting oil was dissolved in 75 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$ solution, H_2O and brine. The organic was dried over Na_2SO_4, filtered and concentrated to give *N*-benzylidene(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (575 mg) as a light yellow solid.

Part B

A solution of *N*-benzylidene(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (575 mg, 1.75 mmol) in 40 mL of MeOH was treated with $NaBH_4$ (250 mg, 6.58 mmol). After stirring for 4 h, the reaction was quenched with saturated $NaHCO_3$ solution and extracted into $CHCl_3$. The organic portion was washed with H_2O and brine and dried over Na_2SO_4. Chromatography (SiO_2, 50-67% EtOAc/hexanes) gave *N*-benzyl(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (427 mg) as a yellow solid.

Part C

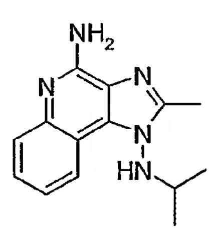
A solution of *N*-benzyl(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (427 mg, 1.29 mmol) in 20 mL of CH_2Cl_2 was treated with MCPBA (77% max., 325 mg, 1.41 mmol). After stirring for 3 h, the reaction was quenched with saturated $NaHCO_3$ solution and extracted into CH_2Cl_2. The organic portion was washed with saturated $NaHCO_3$ solution, H_2O and brine. The organic was dried over Na_2SO_4, filtered and concentrated to give *N*-benzyl(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (393 mg) as a light brown foam.

Part D

A solution of *N*-benzyl(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (393 mg, 1.14 mmol) in 20 mL of 1,2-dichloroethane was placed in a pressure vessel and heated to 70 °C. The rapidly stirred solution was then treated with 5 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (239 mg, 1.25 mmol), the reaction vessel was capped, and heating was continued for 2 h. The reaction mixture was then cooled to ambient temperature and treated with 50 mL of CH_2Cl_2. The reaction mixture was washed with H_2O, 1% Na_2CO_3 solution (3X), H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated. Chromatography (SiO_2, 5% MeOH/$CHCl_3$) followed by crystallization from propyl acetate/hexanes gave N^1-benzyl-2-butyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (237 mg) as light-yellow crystals. mp 159.3-160.5 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 8.31 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.54 (m, 1H), 7.42-7.31 (m, 6H), 5.44 (s, 2H), 5.26 (t, J = 5.6 Hz, 1H), 4.37 (d, J = 5.6 Hz, 2H), 2.71 (t, J = 8.4 Hz, 2H), 1.74 (m, 2H), 1.42 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); MS m/z 346 $(M + H)^+$; Anal. Calcd for $C_{21}H_{23}N_5$: C, 73.02; H, 6.71; N, 20.27. Found: C, 72.75; H, 6.55; N, 20.46.

Example 3

N^1-Isopropyl-2-methyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of *N'*-(3-aminoquinolin-4-yl)hydrazine *tert*-butyl carboxylate (11.67 g, 42.5 mmol) in 400 mL of anhydrous toluene was treated with trimethyl orthoacetate (5.96 mL, 46.8 mmol) and pyridine hydrochloride (100 mg) under an atmosphere of N_2 and heated to reflux. After stirring for 3 h, the reaction mixture was concentrated under reduced pressure to give a red solid. Chromatography (SiO_2, 0-10% MeOH/EtOAc) gave *tert*-butyl *N*-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate (10.7 g) as a yellow foam.

Part B

tert-Butyl *N*-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate (5.00 g, 16.8 mmol) was dissolved in 40 mL of 1.65 M HCl in EtOH, and the reaction mixture was heated to reflux for 2 h. The reaction mixture was cooled and concentrated under reduced pressure to give a brown solid. The brown solid was crystallized from ethanol/H_2O to give 3.13 g of 2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine hydrochloride.

Part C

A suspension of 2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine hydrochloride (1.79 g , 7.62 mmol) in 30 mL of 2,2-dimethoxypropane was treated with 90 mg of *p*-toluenesulfonic acid. The reaction mixture was heated to 100 °C overnight. The reaction mixture was then treated with 10 mL of H_2O and 10 mL of MeOH, and heating was continued for 24 h. The reaction mixture was cooled and concentrated under reduced pressure. The resulting oil was dissolved in 50 mL of $CHCl_3$ and washed with 2% Na_2CO_3 solution, H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated to give *N*-isopropylidene(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (1.82 g) as a yellow solid.

Part D

A solution of *N*-isopropylidene(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (1.82 g, 7.64 mmol) dissolved in 40 mL of MeOH was treated with $NaBH_4$ (1.16 g, 30.6 mmol). After stirring for 18 h, the reaction was quenched with saturated NH_4Cl solution

and partitioned between CH_2Cl_2 and 2% Na_2CO_3 solution. The organic portion was washed with 2% Na_2CO_3 solution, H_2O and brine and dried over Na_2SO_4. The resulting organic portion was filtered and concentrated under reduced pressure to give *N*-isopropyl(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (1.84 g) as a yellow foam.

Part E

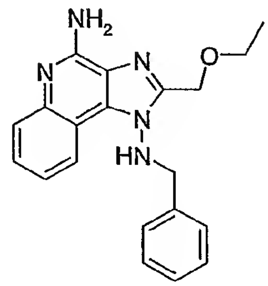
A solution of *N*-isopropyl(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (1.84 g, 7.66 mmol) dissolved in 50 mL of 1,2-dichloroethane was treated with MCPBA (77% max., 2.36 g, 9.58 mmol). After stirring for 3 h, the reaction mixture was treated with 2% Na_2CO_3 solution and extracted into CH_2Cl_2. The organic portion was washed with saturated 2% Na_2CO_3 solution, H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated to give *N*-isopropyl(2-methyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (1.95 g) as a light orange solid.

Part F

A solution of *N*-isopropyl(2-methyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (1.95 g, 7.61 mmol) in 75 mL of CH_2Cl_2 was treated with 35 mL of concentrated NH_4OH solution. To the rapidly stirred solution was added *p*-toluenesulfonyl chloride (1.52 g, 7.99 mmol). After stirring for 30 min, the reaction mixture was treated with $CHCl_3$ (25 mL) and H_2O (35 mL). The layers were separated and the organic portion was washed with 2% Na_2CO_3 solution (2X), H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated to give a light-yellow solid. Crystallization from propyl acetate gave N^1-isopropyl-2-methyl-*1H*-imidazo[4,5-*c*]quinoline-1,4-diamine (747 mg) as off-white crystals. mp 227–229 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, J = 8.2, 1.1 Hz, 1 H), 7.79 (dd, J = 8.4, 0.7 Hz, 1 H), 7.53-7.45 (m, 1 H), 7.33-7.26 (m, 1 H), 5.42 (s, 2 H), 4.91 (d, J = 1.4 Hz, 1 H), 3.73-3.62 (m, 1 H), 2.64 (s, 3 H), 1.15 (d, J = 6.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 151.3, 144.9, 133.3, 127.6, 127.3, 124.6, 122.4, 120.2, 115.4, 52.3, 20.9, 13.8; MS m/z 256 $(M + H)^+$; Anal. Calcd for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43; Found: C, 65.59; H, 6.56; N, 27.09.

Example 4

N^1-Benzyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of *N'*-(3-aminoquinolin-4-yl)hydrazine *tert*-butyl carboxylate (12.15 g, 44.3 mmol) in 200 mL of anhydrous CH_2Cl_2 was cooled to 0 °C and treated with triethylamine (7.72 mL, 55.4 mmol) and 2-ethoxyacetyl chloride (5.70 g, 46.5 mmol) under an atmosphere of N_2. After 3 h, an additional 1 mL of 2-ethoxyacetyl chloride was added. After stirring for 2 h, the reaction mixture was concentrated under reduced pressure to give a brown solid. This was dissolved in 150 mL of EtOH and treated with 18.5 mL of triethylamine, and the mixture was refluxed overnight. The reaction mixture was concentrated under reduced pressure to give a dark-red oil. The red oil was dissolved in 200 mL of CH_2Cl_2 and washed with H_2O (2 X 75 mL) and brine (75 mL). The organic portion was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a red solid. The solid was treated with a minimum amount of hot Et_2O and filtered to remove insoluble material. The filtrate was concentrated to give *tert*-butyl *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate (14.3 g) as a tan solid.

Part B

tert-Butyl *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate (14.3 g, 41.8 mmol) was dissolved in 150 mL of 2 M HCl in EtOH, and the reaction mixture was heated to reflux for 3 h. The reaction mixture was cooled and concentrated under reduced pressure to give a brown solid. The brown solid was dissolved in 100 mL of H_2O and treated with 100 mL of concentrated NH_4OH solution. The basic, aqueous solution was then extracted with CH_2Cl_2 (4X). The combined organic layers were then washed with brine and dried over Na_2SO_4. The solution was filtered and concentrated under reduced

pressure to give a brown foam. The foam was triturated with Et_2O (150 mL) and filtered. The filtrate was concentrated to give 2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-1-amine (5.77 g) as a tan solid.

Part C

A solution of 2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-1-amine (1.50 g, 6.19 mmol) in 50 mL of isopropanol was treated with benzaldehyde (0.66 mL, 6.50 mmol) and 10 mg of *p*-toluenesulfonic acid. The reaction mixture was heated to 120 °C for 3 d. The reaction mixture was cooled, and a precipitate started to form. The reaction mixture was treated with Et_2O and then filtered to give *N*-benzylidene-(2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (1.21 g) as a gray solid.

Part D

A solution of *N*-benzylidene-(2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (1.00 g, 3.03 mmol) in 50 mL of MeOH was treated with $NaBH_4$ (458 mg, 12.1 mmol). After stirring for 1.5 h, the reaction mixture was concentrated, then treated with saturated $NaHCO_3$ solution, and extracted into $CHCl_3$. The organic portion was washed with H_2O and brine and dried over Na_2SO_4. The resulting solution was filtered and concentrated to give *N*-benzyl-(2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (1.01 g) as a tan solid.

Part E

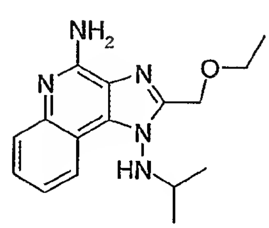
A solution of *N*-benzyl-(2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (1.01 g, 3.04 mmol) in 50 mL of CH_2Cl_2 was treated with MCPBA (77% max., 1.02 g, 4.56 mmol). After stirring for 3 h, the reaction mixture was quenched with 2% Na_2CO_3 solution and extracted into CH_2Cl_2. The organic portion was washed with H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated to give *N*-benzyl-(2-ethoxymethy-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (0.99 g) as a light-yellow solid.

Part F

A solution of *N*-benzyl-(2-ethoxymethy-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (0.99 g, 2.84 mmol) in 50 mL of CH_2Cl_2 was treated with 25 mL of concentrated NH_4OH solution. To the rapidly stirred solution was added *p*-toluenesulfonyl chloride (569 mg, 2.98 mmol). After stirring for 30 min, the reaction was treated with CH_2Cl_2 (50 mL) and H_2O (25 mL). The layers were separated and the organic portion was washed 2% Na_2CO_3 solution, H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated to give a tan solid. Chromatography (SiO_2, 2% MeOH/$CHCl_3$ containing 0.5% concentrated NH_4OH) followed by crystallization from propyl acetate gave N^1-benzyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (148 mg) as white needles. mp 152–155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 (dd, J = 8.2, 1.2 Hz, 1 H), 7.85-7.77 (m, 1 H), 7.59-7.52 (m, 1 H), 7.42-7.34 (m, 4 H), 7.33-7.24 (m, 2 H), 6.02 (t, J = 6.6 Hz, 1 H), 5.39 (s, 2 H), 4.43 (s, 2 H), 4.40 (d, J = 6.7 Hz, 2 H), 3.55 (q, J = 7.0 Hz, 2 H), 1.22 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 147.9, 144.9, 135.7, 129.2, 129.1, 128.6, 127.8, 126.7, 122.4, 120.7, 66.7, 65.3, 56.7, 15.0; MS m/z 348 $(M + H)^+$; Anal. Calcd for $C_{20}H_{21}N_5O \cdot 0.36H_2O$: C, 68.90; H, 6.11; N, 20.09; Found: C, 68.50; H, 6.07; N, 20.11.

Example 5

2-Ethoxymethyl-N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-1-amine (2.50 g, 10.3 mmol) in 250 mL of 1,2-dichloroethane was treated with acetone (0.83 mL, 11.3 mmol), acetic acid (0.65 mL, 11.3 mmol) and sodium triacetoxyborohydride (2.39 g, 11.3 mL). After stirring overnight, additional acetone (5 mL), acetic acid (0.65 mL, 11.3 mmol) and sodium triacetoxyborohydride (2.39 g, 11.3 mL) were added. After 2 d, the reaction was

carefully quenched by addition of saturated $NaHCO_3$ solution. The layers were separated and the aqueous portion was extracted with additional CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a brown oil. Some isopropylidene intermediate was still present, so the material was dissolved in 50 mL of MeOH and treated with $NaBH_4$ (1.0 g). After 2 h, the reaction was quenched by the addition of H_2O and the reaction mixture was concentrated under reduced pressure. The residue was partitioned between saturated $NaHCO_3$ solution and CH_2Cl_2. The layers were separated and the organic portion was washed with saturated $NaHCO_3$, H_2O and brine. The organic portion was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Chromatography (SiO_2, 4% MeOH/$CHCl_3$) gave *N*-(2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (0.98 g) as a brown oil.

Part B

A solution of *N*-(2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (0.98 g, 3.45 mmol) in 35 mL of CH_2Cl_2 was treated with MCPBA (77% max., 1.10 g, 4.48 mmol). After stirring for 3 h, the reaction was quenched with 2% Na_2CO_3 solution and extracted into CH_2Cl_2. The organic portion was washed with H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated to give *N*-(2-ethoxymethy-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (0.93 g) as a light-orange solid.

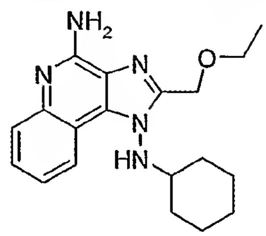
Part C

A solution of *N*-(2-ethoxymethy-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (0.93 g, 3.10 mmol) in 25 mL of CH_2Cl_2 was treated with 15 mL of concentrated NH_4OH solution. To the rapidly stirred solution was added *p*-toluenesulfonyl chloride (620 mg, 3.25 mmol). After stirring for 30 min, the reaction was treated with CH_2Cl_2 (20 mL) and H_2O (15 mL). The layers were separated and the organic portion was washed with 2% Na_2CO_3 solution, H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated to give a tan solid. Chromatography (SiO_2, 5% MeOH/$CHCl_3$) gave 2-ethoxymethyl-N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (368 mg) as a tan solid. mp 162–164 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (dd,

J = 8.2, 1.1 Hz, 1 H), 7.77 (dd, J = 8.4, 0.7 Hz, 1 H), 7.54-7.47 (m, 1 H), 7.33-7.24 (m, 1 H), 5.55 (d, J = 3.2 Hz, 1 H), 5.41 (s, 2 H), 4.89 (s, 2 H), 3.73-3.60 (m, 3 H), 1.26 (t, J = 7.0 Hz, 3H); 1.15 (d, J = 6.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 148.7, 145.0, 127.7, 126.6, 123.9, 121.9, 121.3, 115.4, 66.8, 65.7, 52.5, 20.6, 15.1; MS m/z 300 $(M + H)^+$; Anal. Calcd for $C_{16}H_{21}N_5O \cdot 0.48\ H_2O$: C, 62.39; H, 7.19; N, 22.74; Found: C, 62.38; H, 6.90; N, 22.79.

Example 6

N[1]-Cyclohexyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

2-(Ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine (0.900 g, 3.71 mmol) was placed in a 50 mL round bottom flask, dissolved in 1,2-dichloromethane, and placed under N_2. Cyclohexanone (1.19 mL, 11.5 mmol), acetic acid (0.45 mL, 7.79 mmol) and sodium triacetoxyborohydride (1.65 g, 7.79 mmol) were added and the reaction was stirred under N_2 at room temperature for 5 days. The reaction was quenched by slow addition of saturated $NaHCO_3$ solution (25 mL) and dichloromethane (25 mL). The mixture was transferred to a separatory funnel and the phases separated. The aqueous portion was extracted with dichloromethane (25 mL). The combined organic portions were washed sequentially with water (25 mL) and brine (25 mL), dried (Na_2SO_4), filtered and then concentrated to yield a thick brown oil. Analysis by liquid chromatography/mass spectroscopy (LC/MS) of the crude product showed it to be a mixture of the hydrazone and hydrazine. The oil was dissolved in methanol (25 mL), chilled in an ice water bath and then treated with sodium borohydride (1.25 g). The reaction was quenched with water (25 mL) and the mixture concentrated. The residue was partitioned between dichloromethane 50 mL) and water (15 mL), transferred to a separatory funnel, and the phases were separated. The organic portion was washed sequentially with saturated $NaHCO_3$ solution (20 mL), water (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and

then concentrated to yield a thick brown oil. The material was purified by column chromatography (35 g SiO_2, 97:3 chloroform:methanol) to yield 0.51 g of *N*-cyclohexyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine as a light brown oil / solid.

Part B

N-Cyclohexyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine (0.51 g, 1.57 mmol) was placed in a 200 mL round bottom flask, purged with N_2 and dissolved in dichloromethane (25 mL). MCPBA (0.484 g, 1.96 mmol, 77% max) was added over a 5 min period. The reaction was stirred at room temperature under N_2. After 2 h, analysis by thin layer chromatography (TLC) (SiO_2, 95:5 chloroform:methanol) showed complete conversion. The solution was diluted with dichloromethane (15 mL) and 2% sodium carbonate solution (15 mL). The mixture was transferred to a separatory funnel, and the phases were separated. The organic portion was washed sequentially with 2% sodium carbonate solution (15 mL), water (15 mL) and brine (15 mL), dried (Na_2SO_4), filtered and then concentrated to yield 0.431 g of *N*-cyclohexyl-2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-amine as a tan foam.

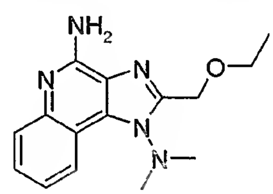
Part C

N-Cyclohexyl-2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-amine (0.425 g, 1.25 mmol) was placed in a 100 mL round bottom flask and dissolved in dichloromethane (20 mL). Ammonium hydroxide solution (10 mL) was added and the mixture was stirred vigorously. The stirred mixture was chilled in an ice water bath. *Para*-toluenesulfonyl chloride (0.250 g, 1.31 mmol) was added over 5 min. After 30 min of stirring at 0 °C TLC (SiO_2, 95:5 chloroform:methanol) showed complete conversion. The mixture was warmed to room temperature and then diluted with dichloromethane (25 mL) and water (10 mL). The mixture was transferred to a separatory funnel and the phases separated. The organic portion was washed sequentially with 2% sodium carbonate solution (15 mL), water (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered and then concentrated to yield an orange/tan foamy solid. The material was purified by column chromatography (40 g SiO_2, 95:5 chloroform:methanol) to yield the product as an off white solid. The off-white solid was dissolved in 3 mL of a 9:1 chloroform:methanol mixture. A small spatula tip full of activated carbon (DARCO G 60-100 mesh) was added

and the mixture was stirred at room temperature for 3 h. The mixture was filtered through a short column of SiO_2 (5 g) eluting with 9:1 chloroform:methanol. The filtrate was concentrated to yield a glassy solid. The glassy solid was triturated in 15 mL diethyl ether for 2 h to provide a white solid. The solid was collected by vacuum filtration and rinsed with diethyl ether. The solid was dried in a vacuum oven (70 °C) to yield 0.062 g of N^1-cyclohexyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine. mp 143–145 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 (dd, J = 8.1, 1.1 Hz, 1 H), 7.58 (dd, J = 8.3, 0.9 Hz, 1 H), 7.46-7.38 (m, 1 H), 7.28-7.21 (m, 1 H), 6.99 (d, J = 1.9 Hz, 1 H), 6.69 (s, 2 H), 4.77 (s, 2 H), 3.63 (q, J = 7.0 Hz, 2 H), 3.32-3.23 (m, 1 H), 1.71-1.52 (m, 5 H), 1.30-1.05 (m, 8 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ; MS *m/z* 152.1, 150.3, 145.0, 133.4, 127.4, 125.8, 123.9, 121.6, 121.1, 115.0, 65.8, 63.1, 59.8, 30.9, 25.8, 24.3, 15.4; MS *m/z* 340 (M + H)$^+$; Anal. Calcd for $C_{19}H_{25}N_5O$: C, 67.23; H, 7.42; N, 20.63; Found: C, 67.32; H, 7.37; N, 20.55.

Example 7

N^1,N^1-Dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 4-chloro-3-nitroquinoline (5.00 g, 24.0 mmol) in 100 mL CH_2Cl_2 was cooled to 0 °C and treated with triethylamine (8.40 mL, 60.0 mmol) and *N,N*-dimethylhydrazine (5.65 mL, 74.4 mmol) under an atmosphere of nitrogen. After 18 h, the mixture was diluted with 2% Na_2CO_3 solution and $CHCl_3$ and separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 4-(2,2-dimethylhydrazino)-3-nitroquinoline (5.33 g) as a yellow/orange crystalline solid.

Part B

A suspension of 4-(2,2-dimethylhydrazino)-3-nitroquinoline (5.33 g, 23.0 mmol) in 125 mL of acetonitrile was treated with 5% platinum on carbon (0.45 g, 0.11 mmol) and the mixture was shaken under an atmosphere of hydrogen (3.8 x 10^5 Pa). After 5 h, the reaction mixture was filtered through a pad of CELITE filter agent and rinsed with 80:20 acetonitrile:MeOH. The filtrate was concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4-(2,2-dimethylhydrazino)quinolin-3-amine (4.64 g) as a red foam.

Part C

A solution of 4-(2,2-dimethylhydrazino)quinolin-3-amine (4.64 g, 23.0 mmol) in 75 mL of CH_2Cl_2 was cooled to 0 °C under an atmosphere of nitrogen. The reaction mixture was treated with triethylamine (6.72 mL, 48.2 mmol) followed by dropwise addition of ethoxyacetyl chloride (2.95 g, 24.1 mmol). After 1.5 h, the reaction mixture was concentrated under reduced pressure. The resulting oil was dissolved in 75 mL of ethanol, treated with triethylamine (9.60 mL, 68.9 mmol) and heated to reflux. After 5 d, the reaction mixture was concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2, washed with 2% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a brown oil. Chromatography (SiO_2, 5-10% MeOH/$CHCl_3$) gave *N,N*-dimethyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine (0.89 g) as a brown oil.

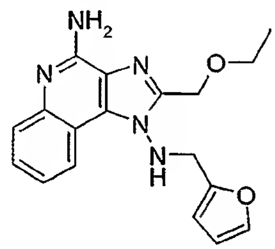
Part D

A solution of *N,N*-dimethyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine (0.89 g, 3.3 mmol) in 25 mL of CH_2Cl_2 was treated with MCPBA (1.01 g, 4.10 mmol, 77% max). After 1.5 h, the reaction mixture was treated with 7 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (0.69 g, 3.6 mmol). After 30 min, the reaction was diluted with CH_2Cl_2 and water and the phases were separated. The organic portion was washed with 2% Na_2CO_3 solution (2X), water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield an orange solid. Recrystallization twice from acetonitrile gave N^1,N^1-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.208 g) as gold, needle-like crystals. mp 213–215

°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (dd, J = 8.3, 1.4 Hz, 1 H), 7.79 (dd, J = 8.4, 0.7 Hz, 1 H), 7.56-7.48 (m, 1 H), 7.38-7.29 (m, 1 H), 5.45 (s, 2 H), 4.48 (s, 2 H), 3.69 (q, J = 7.0 Hz, 2 H), 3.20 (s, 6 H), 1.29 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 149.3, 145.1, 133.5, 127.7, 126.7, 123.8, 122.1, 115.3, 66.4, 65.6, 45.3, 15.1; MS (APCI) m/z 286 $(M + H)^+$; Anal. Calcd for $C_{15}H_{19}N_5O$: C, 63.14; H, 6.71; N, 24.54; Found: C, 63.02; H, 6.91; N, 24.57.

Example 8

2-Ethoxymethyl-N^1-(furan-2-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (1.50 g, 6.19 mmol) in 20 mL of isopropanol was treated with 2-furaldehyde (1.08 mL, 13.0 mmol) and 2 drops of concentrated HCl and heated to reflux under an atmosphere of nitrogen. After 48 h, the reaction was concentrated under reduced pressure to yield a brown oil. The oil was dissolved in 30 mL of $CHCl_3$ and washed with 5% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(furan-2-ylmethylene)amine (1.86 g) as a light brown solid.

Part B

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(furan-2-ylmethylene)amine (1.86 g, 5.81 mmol) in 20 mL of methanol was treated with $NaBH_4$ (0.659 g, 17.4 mmol) and stirred under an atmosphere of nitrogen. After 18 h the reaction was quenched by addition of 20 mL of water. The reaction mixture was concentrated under reduced pressure and dissolved in $CHCl_3$. The organic portion was washed with 2% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under

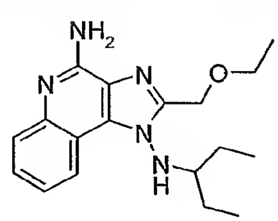
reduced pressure to yield *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(furan-2-ylmethyl)amine (1.70 g) as a thick orange syrup.

Part C

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(furan-2-ylmethyl)amine (1.70 g, 5.27 mmol) in 45 mL of CH_2Cl_2 was treated with MCPBA (1.48 g, 6.59 mmol, 77% max). After 1.5 h the reaction mixture was treated with 15 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (1.06 g, 5.54 mmol). After 45 min the reaction mixture was diluted with water and $CHCl_3$ and separated. The organic portion was washed with 3% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to yield a yellow foam. Chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) gave an off white foam. The foam was triturated with diethyl ether and filtered to give 2-ethoxymethyl-N^1-(furan-2-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (1.03 g) as an off white powder. mp dec. > 200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.80 (dd, *J* = 8.4, 0.8 Hz, 1 H), 7.57-7.51 (m, 1 H), 7.45 (d, *J* = 1.8 Hz, 1 H), 7.39-7.33 (m, 1 H), 6.34-6.32 (m, 1 H), 6.24 (t, *J* = 5.3 Hz, 1 H), 6.07 (d, *J* = 3.1 Hz, 1 H), 5.43 (s, 2 H), 4.40-4.38 (m, 4 H), 3.57 (q, *J* = 7.0 Hz, 2 H), 1.25 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 149.5, 147.8, 144.8, 143.0, 132.6, 127.8, 126.6, 124.1, 122.5, 120.7, 115.1, 111.1, 110.1, 66.8, 64.9, 48.5, 15.0; MS (APCI) *m/z* 338 $(M + H)^+$; Anal. Calcd for $C_{18}H_{19}N_5O_2$: C, 64.08; H, 5.68; N, 20.76; Found: C, 63.89; H, 5.75; N, 20.48.

Example 9

2-Ethoxymethyl-N^1-(1-ethylpropyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (1.50 g, 6.19 mmol) in 20 mL of toluene and 5 mL of isopropanol was treated with 3-pentanone (5.00 mL, 47.2 mmol) and pyridinium *p*-toluenesulfonate (0.015 g, 0.062 mmol) and the reaction mixture was heated to reflux under an atmosphere of nitrogen. After 7 d, the reaction mixture was concentrated under reduced pressure, dissolved in $CHCl_3$, washed with water (2X) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light brown oil. Chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) gave *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(1-ethylpropylidene)amine (1.78 g) as a yellow/green syrup.

Part B

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(1-ethylpropylidene)amine (1.78 g, 5.73 mmol) in 20 mL of methanol was treated with $NaBH_4$ (0.867 g, 22.9 mmol) and $CeCl_3 \cdot 7H_2O$ (15 mg, catalytic) and stirred under an atmosphere of nitrogen. After 24 h, the reaction was concentrated under reduced pressure, dissolved $CHCl_3$, washed with water (2X) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a yellow/green syrup. Chromatography (SiO_2, 93:7 $CHCl_3$:MeOH) gave *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(1-ethylpropyl)amine (1.01 g) as a yellow/green oil.

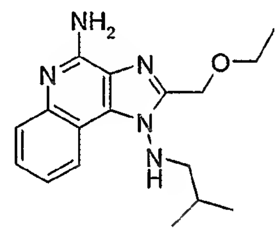
Part C

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(1-ethylpropyl)amine (1.01 g, 3.23 mmol) in 30 mL of CH_2Cl_2 was treated with MCPBA (1.04 g, 4.20 mmol, 77% max). After 1.5 h the reaction mixture was treated with 15 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (0.65 g, 3.39 mmol). After 30 min, the reaction mixture was diluted with CH_2Cl_2 and water and the phases were separated. The organic portion was washed with 2 % Na_2CO_3 solution and water. The combined aqueous washes were back extracted with $CHCl_3$ (2X). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light yellow foam. Chromatography (SiO_2, 97:3 $CHCl_3$:MeOH) gave a white foam. The foam was triturated with CH_2Cl_2/hexanes and

filtered to give 2-ethoxymethyl-N^1-(1-ethylpropyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.652 g) as a white solid. mp 125–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (dd, *J* = 8.3, 1.1 Hz, 1 H), 7.77 (dd, *J* = 7.6, 0.8 Hz, 1 H), 7.55-7.48 (m, 1 H), 7.33-7.26 (m, 1 H), 5.66, (d, *J* = 3.0 Hz, 1 H), 5.41 (s, 2 H), 4.87 (s, 2 H), 3.64 (q, *J* = 7.0 Hz, 2 H), 3.32-3.23 (m, 1 H), 1.70-1.56 (m, 2 H), 1.55-1.41 (m, 2 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 0.94 (t, *J* = 7.5 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 149.1, 145.4, 135.0, 132.4, 128.1, 126.9, 124.1, 122.2, 122.0, 115.9, 67.2, 66.2, 64.0, 24.5, 15.5, 10.2; MS (APCI) *m/z* 328 $(M + H)^+$; Anal. Calcd for $C_{18}H_{25}N_5O$: C, 66.03; H, 7.70; N, 21.39; Found: C, 65.64; H, 7.89; N, 21.02.

Example 10

2-Ethoxymethyl-N^1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (0.940 g, 3.88 mmol) in 20 mL of toluene and 5 mL of isopropanol was treated with isobutyraldehyde (0.800 mL, 8.81 mmol) and pyridinium *p*-toluenesulfonate (0.098 g, 0.39 mmol) and the reaction mixture was heated to reflux under an atmosphere of nitrogen. After 48 h, the reaction mixture was concentrated under reduced pressure and dissolved in $CHCl_3$. The organic portion was washed with water (2X) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light brown oil which solidified under vacuum to yield *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isobutylideneamine (1.15 g) as a tan solid.

Part B

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isobutylideneamine (1.15 g, 3.88 mmol) in 15 mL of methanol was treated with $NaBH_4$

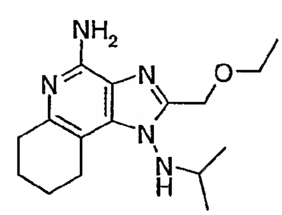
(0.44 g, 11.6 mmol) and stirred under an atmosphere of nitrogen. After 18 h, the reaction was concentrated under reduced pressure. The residue was partitioned between $CHCl_3$ and water, and the phases were separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield an orange oil. Chromatography (SiO_2, 97:3 $CHCl_3$:MeOH), gave *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isobutylamine (0.69 g) as clear, colorless crystals.

Part C

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isobutylamine (1.16 g, 3.89 mmol) in 30 mL of CH_2Cl_2 was treated with MCPBA (1.25 g, 5.05 mmol, 77% max). After 1.5 h, the reaction mixture was treated with 15 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (0.78 g, 4.08 mmol). After 30 min the reaction mixture was diluted with CH_2Cl_2 and water, and the phases were separated. The organic portion was washed with 2% Na_2CO_3 solution and water. The combined aqueous washes were back extracted with $CHCl_3$ (2X). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a brown foam. Chromatography (SiO_2, 97:3 $CHCl_3$:MeOH) yielded 2-ethoxymethyl-N^1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.049 g) as an off white solid. mp 137–140 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 350 K) δ 8.47 (dd, J = 8.1, 0.9 Hz, 1 H), 7.60 (d, J = 8.3 Hz, 1 H), 7.45-7.36 (m, 1 H), 7.28-7.19 (m, 1 H), 6.67, (t, J = 6.2 Hz, 1 H), 6.22 (s, 2 H), 4.76 (s, 2 H), 3.64 (q, J = 7.0 Hz, 2 H), 3.02 (t, J = 6.4 Hz, 2 H), 1.97 (s, J = 6.7 Hz, 1 H), 1.19 (t, J = 7.0 Hz, 3 H), 1.05 (d J = 6.7 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.9, 148.9, 144.8, 131.9, 126.9, 125.7, 123.8, 120.8, 114.2, 65.4, 62.8, 59.6, 26.7, 20.5, 14.9; MS (APCI) m/z 314 $(M + H)^+$; Anal. Calcd for $C_{17}H_{23}N_5O$: C, 65.15; H, 7.40; N, 22.35; Found: C, 64.88; H, 7.39; N, 22.38.

Example 11

2-Ethoxymethyl-N^1-isopropyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine

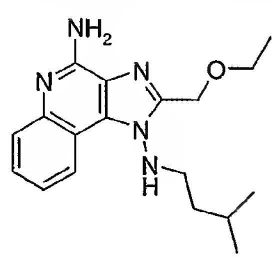


Part A

A solution of 2-ethoxymethyl-*N*[1]-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.700 g, 2.34 mmol) in 25 mL of trifluroacetic acid was treated with platinum(IV) oxide (0.27 g, 1.2 mmol) and the mixture was shaken under an atmosphere of hydrogen (3.8 x 10^5 Pa). After 15 h, the reaction mixture was filtered through a pad of CELITE filter agent, rinsed with 9:1:0.5 $CHCl_3$:MeOH:trifluoroacetic acid (TFA) and concentrated under reduced pressure to yield a creamy white solid. The solid was triturated with concentrated NH_4OH solution for 2 h and then extracted with $CHCl_3$ (3X). The organic portion was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a white foam. The foam was triturated with diethyl ether, filtered and dried under reduced pressure to yield 2-ethoxymethyl-*N*[1]-isopropyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.376 g) as a fine white solid. mp 144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (d, J = 2.7 Hz, 1 H), 4.92 (s, 2 H), 4.78 (s, 2 H), 3.61 (q, J = 7.0 Hz, 2 H), 3.53-3.43 (m, 1 H), 3.07-3.03 (m, 2 H), 2.85-2.81 (m, 2 H), 1.92-1.79 (m, 4 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.08 (d, J = 6.3 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 148.9, 148.1, 138.8, 122.9, 107.4, 66.6, 65.4, 53.0, 32.5, 23.7, 23.2, 22.8, 20.5, 15.1; MS (APCI) *m/z* 304 $(M + H)^+$; Anal. Calcd for $C_{16}H_{25}N_5O$: C, 63.34; H, 8.31; N, 23.08; Found: C, 63.32; H, 8.31; N, 22.97.

Example 12

2-Ethoxymethyl-*N*[1]-(3-methylbutyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (1.00 g, 4.13 mmol) in 20 mL of toluene and 5 mL of isopropanol was treated with isovaleraldehyde (0.94 mL, 8.76 mmol) and pyridinium *p*-toluenesulfonate (0.052 g, 0.21 mmol) and the

reaction mixture was heated to reflux under an atmosphere of nitrogen. After 15 h, the reaction mixture was concentrated under reduced pressure to yield a brown oil. The oil was dissolved in $CHCl_3$ and washed with water (2X) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(3-methylbutylidene)amine (1.28 g) as a dark orange oil.

Part B

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(3-methylbutylidene)amine (1.28 g, 4.13 mmol) in 25 mL of methanol was treated with $NaBH_4$ (0.47 g, 12.39 mmol). After 1 h, the reaction was quenched with saturated NH_4Cl solution and the mixture was concentrated under reduced pressure. The residue was partitioned between $CHCl_3$ and saturated $NaHCO_3$ solution and the phases were separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(3-methylbutyl)amine (1.24 g) as a dark orange oil.

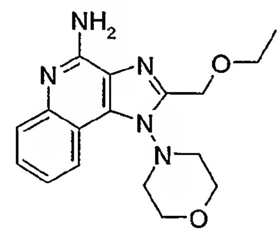
Part C

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(3-methylbutyl)amine (1.24 g, 3.97 mmol) in 45 mL of CH_2Cl_2 was treated with MCPBA (1.87 g, 7.04 mmol, 77% max). After 1.5 h, the reaction mixture was treated with 15 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (0.795 g, 4.17 mmol). After 30 min, the reaction mixture was diluted with $CHCl_3$ and water and the phases were separated. The organic portion was washed with 5% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a sticky orange foam. Chromatography (SiO_2, 97:3 $CHCl_3$:MeOH) gave an off white foam. The foam was triturated with diethyl ether and hexanes and filtered to give 2-ethoxymethyl-N^1-(3-methylbutyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.435 g) as a cream colored solid. mp 129–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, J = 8.1, 1.1 Hz, 1 H), 7.78 (d, J = 8.3 Hz, 1 H), 7.56-7.50 (m, 1 H), 7.36-7.30 (m, 1 H), 5.59 (t, J = 6.7 Hz, 1 H), 5.42 (s, 2 H), 4.87 (s, 2 H), 3.64 (q, J = 7.0 Hz, 2 H), 3.29 (q, J = 7.0 Hz, 2 H), 1.76 (s, J = 6.7 Hz, 1 H), 1.60 (q, J = 6.9 Hz, 2 H), 1.27 (t, J = 7.0 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 147.8, 144.9, 133.1, 127.8, 126.6, 124.0, 122.3, 120.7,

115.2, 66.8, 65.3, 51.1, 36.7, 26.0, 22.6, 15.1; MS (APCI) *m/z* 328 $(M + H)^+$; Anal. Calcd for $C_{18}H_{25}N_5O{\cdot}0.06H_2O$: C, 65.81; H, 7.71; N, 21.32; Found: C, 65.42; H, 7.75; N, 21.11. Karl Fischer analysis 0.32% water.

Example 13

2-Ethoxymethyl-1-(morpholin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A solution of 4-chloro-3-nitroquinoline (5.00 g, 24.0 mmol) in 100 mL of CH_2Cl_2 was treated with triethylamine (6.37 mL, 48.0 mmol) and 4-aminomorpholine (3.47 mL, 36.0 mL) under an atmosphere of nitrogen. After 15 h, the reaction mixture was diluted with 5% Na_2CO_3 solution and $CHCl_3$, and the phases were separated. The organic portion was washed with another portion of 5% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a bright yellow solid. Recrystallization from acetonitrile gave *N*-(morpholin-4-yl)(3-nitroquinolin-4-yl)amine (4.54 g) as bright yellow needle-like crystals.

Part B

A solution of *N*-(morpholin-4-yl)(3-nitroquinolin-4-yl)amine (4.54 g, 16.6 mmol) in 150 mL of toluene was treated with 5% platinum on carbon (0.65 g, 0.17 mmol) and the mixture was shaken under an atmosphere of hydrogen (3.8×10^5 Pa). After 15 h, the reaction mixture was filtered through a pad of CELITE filter agent and rinsed with 4:1 toluene:MeOH. The filtrate was concentrated under reduced pressure to yield N^4-(morpholin-4-yl)quinoline-3,4-diamine (4.06 g) as a red foam.

Part C

A solution of N^4-(morpholin-4-yl)quinoline-3,4-diamine (4.06 g, 16.6 mmol) in 50 mL of CH_2Cl_2 was treated with triethylamine (4.40 mL, 33.2 mmol) and cooled to 0 °C. The solution was treated dropwise with ethoxyacetyl chloride (2.40 g, 17.4 mmol) and stirred under an atmosphere of nitrogen. The reaction mixture was allowed to slowly come to room temperature. After 2 d, the reaction mixture was concentrated under reduced pressure to yield a red semi-solid. The material was dissolved in $CHCl_3$ and washed with water, 5% Na_2CO_3 solution and brine, dried over Na_2SO_4, filtered and dried to yield 2-ethoxy-*N*-{4-[(morpholin-4-yl)amino]quinolin-3-yl}acetamide (5.35 g) as a red/orange foam.

Part D

A suspension of 2-ethoxy-*N*-{4-[(morpholin-4-yl)amino]quinolin-3-yl}acetamide (5.35 g, 16.2 mmol) in 65 mL of toluene was treated with pyridine hydrochloride (0.94 g g, 0.081 mmol). The reaction flask was equipped with a Dean-Stark trap and the reaction mixture was heated to reflux under an atmosphere of nitrogen. After 2.5 d, the reaction mixture was concentrated under reduced pressure to yield a brown oil. The oil was dissolved in $CHCl_3$ and was washed with 5% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a brown foam. Chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) gave 2-ethoxymethyl-1-(morpholin-4-yl)-1*H*-imidazo[4,5-*c*]quinoline (1.61 g) as a light brown solid.

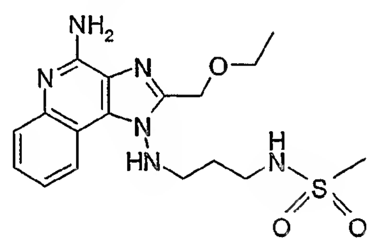
Part E

A solution of 2-ethoxymethyl-1-(morpholin-4-yl)-1*H*-imidazo[4,5-*c*]quinoline (1.61 g, 5.51 mmol) in 40 mL of CH_2Cl_2 was treated with MCPBA (1.78 g, 6.70 mmol, 77% max). After 30 min, the reaction mixture was treated with 20 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (1.03 g, 5.41 mmol). After 15 min, the reaction mixture was diluted with CH_2Cl_2 and water and the phases were separated. The organic portion was washed with 5% Na_2CO_3 solution,. water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a tan foam. Chromatography (SiO_2, 97:3 $CHCl_3$:MeOH) gave a light yellow foam. The foam was triturated with diethyl ether and filtered to give 2-ethoxymethyl-1-(morpholin-4-yl)-1*H*-

imidazo[4,5-*c*]quinolin-4-amine (0.794 g) as a light cream colored solid. mp 223–224 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, *J* = 8.1 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 7.54 (t, *J* = 8.2 Hz, 1 H), 7.34 (t, *J* = 8.1 Hz, 1 H), 5.48 (s, 2 H), 4.85 (s, 2 H), 4.06-4.03 (m, 4 H), 3.74-3.66 (m, 4 H), 3.42-3.38 (m, 2 H), 1.29 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 149.0, 145.3, 133.5, 127.9, 126.9, 123.7, 122.2, 121.3, 115.3, 67.5, 66.5, 65.9, 53.5, 15.1; MS (APCI) *m/z* 328 $(M + H)^+$; Anal. Calcd for $C_{17}H_{21}N_5O_2$: C, 62.37; H, 6.47; N, 21.39; Found: C, 62.14; H, 6.19; N, 21.34.

Example 14

N-{3-[(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl} methanesulfonamide



Part A

A solution of 1-amino-3,3-diethoxypropane (5.00 mL, 30.9 mmol) in 5 mL of tetrahydrofuran (THF) was treated with triethylamine (4.51 mL, 34.0 mmol) under an atmosphere of nitrogen and cooled to 0 °C. The reaction mixture was then treated dropwise with a solution of di-*tert*-butyl dicarbonate (7.42 g, 34.0 mmol) in 25 mL of THF. The reaction mixture was stirred for 2 h at 0 °C and then allowed to come to room temperature. After 15 h, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water (2X) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *tert*-butyl (3,3-diethoxypropyl)carbamate (8.40 g) as a clear, faintly yellow oil.

Part B

A solution of 2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (1.00 g, 4.13 mmol) in 20 mL of acetonitrile and 5 mL of glacial acetic acid was treated with *tert*-butyl (3,3-diethoxypropyl)carbamate (2.55 g, 10.3 mmol) and heated to reflux under an

atmosphere of nitrogen. After 15 h, the reaction mixture was concentrated under reduced pressure to yield a brown oil. The oil was partitioned between $CHCl_3$ and saturated $NaHCO_3$ solution and the phases were separated. The organic portion was washed with water (2X) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *tert*-butyl {3-[(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)imino]propyl}carbamate (1.64 g) as a dark red/orange oil.

Part C

A solution of *tert*-butyl {3-[(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)imino]propyl}carbamate (1.64 g, 4.13 mmol) in 20 mL of methanol was treated with $NaBH_4$ (0.78 g, 20.6 mmol) under an atmosphere of nitrogen. After 1.5 h, the reaction mixture was quenched with saturated NH_4Cl solution and concentrated under reduced pressure. The residue was partitioned between saturated $NaHCO_3$ solution and $CHCl_3$ and the phases were separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light brown solid. Chromatography [SiO_2, 95:5 $CHCl_3$:(80:18:2 $CHCl_3$:MeOH:NH_4OH)] yielded *tert*-butyl {3-[(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}carbamate (1.34 g) as a tan foam.

Part D

A solution of *tert*-butyl {3-[(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}carbamate (1.34 g, 3.35 mmol) in 30 mL of $CHCl_3$ was treated with MCPBA (1.45 g, 5.03 mmol, 77% max). After 3 h, the reaction mixture was diluted with 10% Na_2CO_3 solution and $CHCl_3$ and the phases were separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *tert*-butyl {3-[(2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}carbamate (1.39 g) as an orange foam.

Part E

A solution of *tert*-butyl {3-[(2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}carbamate (1.39 g, 3.35 mmol) in 35 mL of $CHCl_3$ was treated with 15 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (0.67 g, 3.51 mmol).

After 15 min, the reaction mixture was diluted with water and $CHCl_3$ and the phases were separated. The organic portion was washed with 10% Na_2CO_3 solution and water. The combined aqueous washes were back-extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield {3-[(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl} *tert*-butyl carbamate (1.30 g) as an orange foam.

Part F

A solution of {3-[(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl} *tert*-butyl carbamate (1.30 g, 3.14 mmol) in 10 mL of ethanol was treated with a solution of 3 M hydrogen chloride in ethanol (5.0 mL, 15 mmol) and heated to 100 °C. After 30 min, the solvent was concentrated under reduced pressure to yield a brown sludge. The material was triturated with diethyl ether and filtered to give a tan solid. The solid was dissolved in water and treated with 10% NaOH solution until pH 13 was reached. The aqueous solution was extracted with CH_2Cl_2 (4X). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield N^1-(3-aminopropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.77 g) as a gold colored foam.

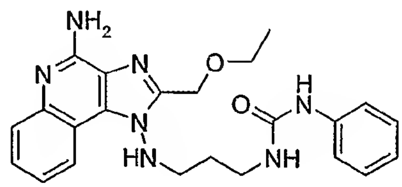
Part G

A solution of N^1-(3-aminopropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.250 g, 0.795 mmol) in 10 mL of CH_2Cl_2 was treated with triethylamine (0.221 mL, 1.67 mmol) under an atmosphere of nitrogen and cooled to 0 °C. The reaction mixture was treated dropwise with methanesulfonyl chloride (0.065 mL, 0.835 mmol). After 16 h, the reaction mixture was quenched by 10% Na_2CO_3 solution, diluted with $CHCl_3$ and the phases were separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light yellow solid. Chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) gave an off-white foam. The foam was triturated with diethyl ether and filtered to give *N*-{3-[(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}methanesulfonamide (0.164 g) as an off white solid. mp 148–150 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (d, J = 7.8 Hz, 1 H), 7.58 (d, J = 8.2 Hz, 1 H), 7.44 (t, J = 7.1 Hz, 1 H), 7.25 (t, J = 7.4 Hz, 1 H),

7.05-6.95 (m, 2 H), 6.61 (s, 2 H), 4.76 (s, 2 H), 3.62 (q, J = 7.0 Hz, 2 H), 3.22 (q, J = 6.8 Hz, 2 H), 3.07 (q, J = 6.2 Hz, 2 H), 2.88 (s, 3 H), 1.78 (p, J = 6.3 Hz, 2 H), 1.18 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.3, 149.5, 145.3, 132.5, 127.4, 126.1, 124.2, 121.3, 121.3, 114.7, 65.9, 63.1, 49.9, 39.6, 28.1, 15.4; MS (APCI) *m/z* 393 (M + H)$^+$; Anal. Calcd for $C_{17}H_{24}N_6O_3$: C, 52.03; H, 6.16; N, 21.41; Found: C, 51.84; H, 6.28; N, 21.18.

Example 15

1-{3-[(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}-3-phenylurea



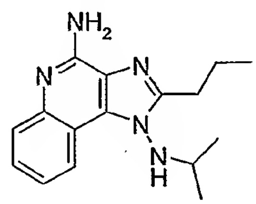
Part A

A solution of N^1-(3-aminopropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.250 g, 0.795 mmol) in 10 mL of CH_2Cl_2 was cooled to 0 °C under an atmosphere of nitrogen. The reaction mixture was treated dropwise with phenyl isocyanate (0.091 mL, 0.835 mmol). After 16 h, the reaction mixture was quenched by 10% Na_2CO_3 solution, diluted with $CHCl_3$ and the phases were separated. The organic portion was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield an off-white solid. Chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) gave an off-white foam. The foam was triturated with diethyl ether and filtered to give 1-{3-[(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}-3-phenylurea (0.115 g) as an off-white solid. mp 177–179 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (dd, J = 8.1, 1.0 Hz, 1 H), 8.39 (s, 1 H), 7.58 (dd, J = 8.4, 0.9 Hz, 1 H), 7.44-7.35 (m, 3 H), 7.25-7.18 (m, 3 H), 6.99 (t, J = 5.6 Hz, 1 H), 6.90-6.85 (m, 1 H), 6.60 (s, 2 H), 6.16 (t, J = 5.6 Hz, 1 H), 4.76 (s, 2 H), 3.60 (q, J = 7.0 Hz, 2 H), 3.26-3.18 (m, 4 H), 1.76 (t, J = 7.0 Hz, 2 H), 1.15 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.2, 151.8, 149.0, 144.8, 140.4, 132.0, 128.5, 126.9, 125.7, 123.7, 120.9, 120.8, 120.8,

117.6, 114.3, 65.4, 62.7, 49.7, 37.0, 28.1, 14.9; MS (APCI) m/z 434 $(M + H)^+$; Anal. Calcd for $C_{23}H_{27}N_7O_2$: C, 63.72; H, 6.28; N, 22.62; Found: C, 63.45; H, 6.04; N, 22.28.

Example 16

N^1-Isopropyl-2-propyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A suspension of *N'*-(3-aminoquinolin-4-yl)hydrazine *tert*-butyl carboxylate (6.50 g, 23.7 mmol) in 100 mL of toluene was treated with trimethyl orthobutyrate (4.18 mL, 26.1 mmol) and pyridine hydrochloride (0.14 g, 1.2 mmol) and heated to 130 °C under an atmosphere of nitrogen. After 18 h, the reaction mixture was concentrated under reduced pressure to yield a brown oil. The oil was dissolved in 150 mL $CHCl_3$, washed with water (2 X 50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 7.23 g of *tert*-butyl (2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate as an orange foam.

Part B

A solution of *tert*-butyl (2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate (7.23 g, 22.2 mmol) in 40 mL of ethanol was treated with HCl (37 mL, 111 mmol, 3 M in ethanol) and heated to reflux. After 1 h, the reaction mixture was cooled to ambient temperature, diluted with 80 mL of diethyl ether, and cooled in an ice water bath. The HCl salt of the product was collected by vacuum filtration and rinsed with diethyl ether until the filtrate ran clear. The dried HCl salt was dissolved in 75 mL of water and treated with 50% NaOH solution until the pH of the water was 12-13. The free base of the product precipitated out and was triturated in the basic water for 30 min while being cooled in an ice water bath. The solid was collected by vacuum filtration and dried under vacuum to give 4.64 g of 2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine as a tan granular solid.

Part C

A solution of 2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (4.64 g, 20.5 mmol) in 60 mL of acetonitrile and 15 mL of glacial acetic acid was treated with 2,2-dimethoxypropane (12.6 mL, 103 mmol) and heated to 100 °C under an atmosphere of nitrogen. After 6 d, the reaction mixture was concentrated under reduced pressure to yield a brown oil. The oil was dissolved in 100 mL of $CHCl_3$ and washed with 10% Na_2CO_3 (2 X 25 mL), water (25 mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4.30 g of *N*-isopropylidene-(2-propyl-1*H*-imidazo[4,5-c]quinolin-1-yl)amine as a brown oil.

Part D

A solution of *N*-isopropylidene-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (4.30 g, 16.1 mmol) in 100 mL of methanol was cooled in an ice water bath. The solution was treated with sodium borohydride (3.05 g, 80.7 mmol) over 5 min. The reaction mixture was allowed to warm to ambient temperature. After 2.5, the reaction was quenched by addition of 15 mL of saturated NH_4Cl solution. The mixture was concentrated under reduced pressure to yield a light brown solid. The solid was partitioned between 100 mL $CHCl_3$ and 25 mL of saturated $NaHCO_3$ solution and then separated. The organic portion was washed with water (25 mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light brown solid. The solid was purified by chromatography (SiO_2, 97:2.5:0.5 $CHCl_3$:MeOH:NH_4OH) to give 2.48 g of *N*-isopropyl-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine as a tan solid.

Part E

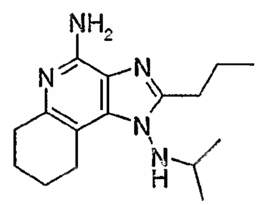
A solution of *N*-isopropyl-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (2.48 g, 9.24 mmol) in 75 mL of chloroform was cooled in a cold water bath. The solution was treated with MCPBA (3.32 g, 11.6 mmol) over 6 min. The reaction was allowed to come to ambient temperature. After 1.5 h, TLC showed complete conversion to the 5-*N*-oxide intermediate. The reaction mixture was again cooled in a cold water bath and then treated with concentrated ammonium hydroxide solution (30 mL, 30%) and stirred rapidly. The reaction mixture was treated with *p*-toluenesulfonyl chloride (1.85 g, 9.70 mmol) over 5 min. The reaetion was allowed to come to ambient temperature. After 30 min, the

reaction mixture was diluted with 50 mL of chloroform and 30 mL of water and the phases were separated. The organic portion was washed with 5% Na_2CO_3 solution (30 mL), water (30 mL) and brine (30 mL). The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light brown foam. The material was purified by chromatography (SiO_2, 97:3 $CHCl_3$:MeOH) and recrystallized from EtOAc to yield 1.39 g of *N*^{1}-isopropyl-2-propyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine as amber crystals.

mp 181–184 °C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.44 (d, *J* = 8.1 Hz, 1 H), 7.57 (d, *J* = 8.3 Hz, 1 H), 7.41-7.35 (m, 1 H), 7.23-7.18 (m, 1 H), 6.95 (d, *J* = 1.6 Hz, 1 H), 6.48 (s, 2 H), 3.52-3.45 (m, 1 H), 2.98-2.85 (m, 2 H), 1.91-1.79 (m, 2 H), 1.03-0.98 (m, 9 H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 154.5, 152.0, 144.9, 132.6, 126.8, 126.1, 124.2, 121.2, 120.9, 115.0, 51.2, 28.2, 21.1, 20.6, 14.3; MS (APCI) *m/z* 284 $(M + H)^+$; Anal. Calcd for $C_{16}H_{21}N_5$: C, 67.82; H, 7.47; N, 24.71; Found: C, 67.66; H, 7.39; N, 24.66.

Example 17

N^1-Isopropyl-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



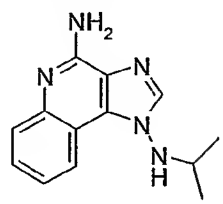
Part A

A solution of *N*^{1}-isopropyl-2-propyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.59 g, 2.1 mmol) in 15 mL of trifluoroacetic acid was treated with platinum(IV) oxide (0.55 g, 2.4 mmol) and shaken under an atmosphere of hydrogen (3.8×10^5 Pa). After 6 days, the reaction mixture was filtered through a pad of CELITE filter agent and rinsed with a mixture of 85:15:0.1 $CHCl_3$:MeOH:TFA until the filtrate ran clear. The filtrate was concentrated under reduced pressure to yield a white foam. The material was suspended in water and treated with 50 % NaOH solution until the pH reached 13. A white solid precipitated and was triturated in the basic mixture for 1 h. The white solid was collected by vacuum filtration. The solid was purified by chromatography (SiO_2, 95:5:0.1 $CHCl_3$:MeOH:NH_4OH) to yield 0.23 g of *N*^{1}-isopropyl-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine as a white solid.

mp 162–164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.34 (s, 1 H), 5.64 (s, 2 H), 3.38-3.23 (m, 2 H), 2.85-2.79 (m, 3 H), 2.78-2.71 (m, 2 H), 1.84-1.71 (m, 6 H), 0.99-0.86 (m, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.4, 149.3, 146.1, 137.9, 122.8, 105.7, 52.4, 32.5, 28.4, 23.3, 23.1, 22.9, 21.0, 20.7, 14.3; MS (APCI) *m/z* 288 $(M + H)^+$; Anal. Calcd for $C_{16}H_{25}N_5$: C, 66.87; H, 8.77; N, 24.37; Found: C, 66.65; H, 8.90; N, 24.08.

Example 18

N^1-Isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A suspension of *N'*-(3-aminoquinolin-4-yl)hydrazine *tert*-butyl carboxylate (6.50 g, 23.7 mmol) in 100 mL of toluene was treated with triethyl orthoformate (8.68 mL, 52.2 mmol) and pyridine hydrochloride (0.14 g, 1.2 mmol) and heated to 130 °C under an atmosphere of nitrogen. After 23 h, the reaction mixture was concentrated under reduced pressure to yield a red/brown oil. The oil was dissolved in $CHCl_3$ (150 mL) and washed with water (2 X 50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 6.74 of *tert*-butyl *N*-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate as a red/orange oil.

Part B

A solution of *tert*-butyl *N*-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate (6.74 g, 23.7 mmol) in 40 mL of ethanol was treated with 40 mL of HCl (40 mL, 119 mmol, 3 M in ethanol) and heated to reflux. After 1 h, the reaction mixture was cooled to ambient temperature, diluted with 80 mL of diethyl ether, and cooled in an ice water bath which precipitated a tan solid. The HCl salt of the product was collected by vacuum filtration and rinsed with diethyl ether until the filtrate ran clear. The dried HCl salt was dissolved in 75 mL of water and made basic by addition of 50% NaOH solution until the pH of the water was 12-13. The free base of the product precipitated out and was triturated in the basic water for 30 min while being cooled in an ice water bath. The solid was collected by

vacuum filtration and dried under vacuum to give 2.86 g of 1*H*-imidazo[4,5-*c*]quinolin-1-amine as a tan granular solid.

Part C

A solution of 1*H*-imidazo[4,5-*c*]quinolin-1-amine (2.86 g, 15.5 mmol) in 60 mL of acetonitrile and 15 mL of glacial acetic acid was treated with 2,2-dimethoxypropane (9.53 mL, 77.5 mmol) and heated to 100 °C under an atmosphere of nitrogen. After 18 h, the reaction mixture was concentrated under reduced pressure to give a brown oil. The oil was dissolved in 100 mL of $CHCl_3$ and washed with 5% Na_2CO_3 solution (2 X 30 mL), water (30 mL) and brine (30 mL). The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 3.48 g of *N*-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine as a brown oil.

Part D

A solution of *N*-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine (3.48 g, 15.5 mmol) in 75 mL of methanol was cooled in an ice water bath. The solution was treated over 5 min with sodium borohydride (2.94 g, 77.6 mmol). After 1 h, the reaction mixture was quenched with 20 mL of saturated NH_4Cl solution and then concentrated under reduced pressure to yield a brown soild. The solid was partitioned between 80 mL $CHCl_3$ and 20 mL saturated $NaHCO_3$ solution and the phases were separated. The organic portion was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown solid. The solid was purified by chromatography (SiO_2, 95:5:0.5 $CHCl_3$:MeOH:NH_4OH) to give 1.28 g of *N*-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine as a tan foam.

Part E

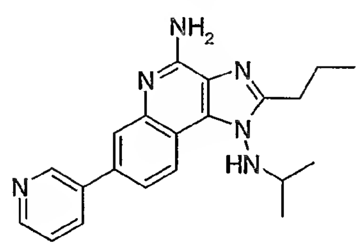
A solution of *N*-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (1.36 g, 5.66 mmol) in 50 mL of chloroform was cooled in a cold water bath. The solution was treated with MCPBA (2.03 g, 7.07 mmol) over 5 min and then allowed to warm to ambient temperature. After 1 h, TLC showed complete conversion to the intermediate 5-*N*-oxide. The reaction mixture was again cooled with a cold water bath. The solution was treated with concentrated ammonium hydroxide solution (25 mL, 30%) and stirred rapidly to

homogenize. The reaction mixture was treated with *p*-toluenesulfonyl chloride (1.13 g, 5.94 g) over 5 min and allowed to warm to ambient temperature. After 30 min, the reaction mixture was diluted with 50 mL of $CHCl_3$ and 25 mL of water. An undissolved solid between the phases was filtered off, saved, and the phases were separated. The organic portion was washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL) and brine (30 mL). The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a tan/orange solid. A high-performance liquid chromatography (HPLC) analysis of the filtered solid matched that of the solid from the concentrated organic extracts. The combined solid was recrystallized twice from MeOH to give 1.18 g of N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine as an off-white solid.

mp dec. > 250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 (dd, J = 8.1, 1.1 Hz, 1 H), 8.23 (s, 1 H), 7.56 (d, J = 7.6 Hz, 1 H), 7.43-7.37 (m, 1 H), 7.23-7.18 (m, 1 H), 7.04 (d, J = 3.4 Hz, 1 H), 6.58 (s, 2 H), 3.57-3.47 (m, 1 H), 1.03 (d, J = 6.2 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.4, 145.3, 132.3, 127.3, 126.0, 125.1, 121.5, 121.0, 115.1, 52.6, 20.6; MS (APCI) *m/z* 242 $(M + H)^+$; Anal. Calcd for $C_{13}H_{15}N_5$: C, 64.71; H, 6.27; N, 29.02; Found: C, 63.11; H, 6.30; N, 27.96.

Example 19

N^1-Isopropyl-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A suspension of 7-bromo-4-chloro-3-nitroquinoline (75.00 g, 260.9 mmol) in 350 mL of dichloromethane was cooled to 0 °C under an atmosphere of nitrogen. The suspension was treated with triethylamine (43.25 mL, 326.1 mmol), which dissolved most of the material. A solution of *tert*-butyl carbazate (37.93 g, 287.0 mmol) in 250 mL of dichloromethane was added to the reaction mixture over 20 min. The reaction was allowed to slowly come to ambient temperature. After 15 h, the reaction mixture was

washed with 5% Na_2CO_3 solution (2 X 100 mL) and water (100 mL). The combined aqueous washes were back-extracted with $CHCl_3$ (50 mL). The combined organic portions were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 99.98 g of *N'*-(7-bromo-3-nitroquinolin-4-yl)hydrazine *tert*-butyl carboxylate as a dark red solid.

Part B

A suspension of *N'*-(7-bromo-3-nitroquinolin-4-yl)hydrazine *tert*-butyl carboxylate (50.0 g, 131 mmol) in 320 mL of acetonitrile (MeCN) and 80 mL of methanol was treated with platinum on carbon (5.0 g, 1.3 mmol, 5% w/w) and shaken under an atmosphere of hydrogen (3.8 x 10^5 Pa). After 4 h, the reaction mixture was filtered through a pad of CELITE filter agent and rinsed with portions of MeCN:MeOH (1:1) until the filtrate ran clear. The filtrate was concentrated under reduced pressure to yield 37.1 g of *N'*-(3-amino-7-bromoquinolin-4-yl)hydrazine *tert*-butyl carboxylate as a tan solid.

Part C

A solution of *N'*-(3-amino-7-bromoquinolin-4-yl)hydrazine *tert*-butyl carboxylate (37.1 g, 105 mmol) in 315 mL of toluene was treated with trimethyl orthobutyrate (16.7 mL, 105 mmol) and pyridine hydrochloride (0.12 g, 1.05 mmol). The reaction mixture was heated to reflux under an atmosphere of nitrogen. After 4 h, the reaction mixture was cooled to ambient temperature and concentrated under reduced pressure to give a brown oil. The oil was dissolved in 300 mL of $CHCl_3$. The solution was washed with 5% Na_2CO_3 (100 mL), water (100 mL) and brine (100 mL). The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a brown foam. The foam was purified by chromatography (SiO_2, 100:0 gradient to 95:5 $CHCl_3$:MeOH) to yield 30.1 g of (7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) *tert*-butyl carbamate as a light brown solid.

Part D

A suspension of (7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) *tert*-butyl carbamate (30.1 g, 74.3 mmol) in 25 mL of ethanol was treated with HCl in ethanol (86.4 mL, 37.1 mmol, 4.3 M) and heated to 100 °C. After 30 min, the reaction mixture was

cooled to ambient temperature and concentrated under reduced pressure to yield a brown solid. The solid was suspended in 100 mL of water, stirred vigorously and treated with 50% NaOH solution until the pH of the liquid rose to 12-13. A brown solid collected around the stir bar. The water was diluted with 200 mL of dichloromethane and the solid was broken apart. The material was triturated in the biphasic mixture overnight. After triturating for 15 h, the mixture was filtered to give the crude free base as a light brown solid. The solid was dried under vacuum to give 17.6 g of 7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine as a light brown solid.

Part E

A suspension of 7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (17.6 g, 57.7 mmol) in 160 mL of acetonitrile and 40 mL of glacial acetic acid was treated with 2,2-dimethoxypropane (35.5 mL, 288 mmol). The reaction mixture was heated to 100° C under an atmosphere of nitrogen. After 16 h, the reaction was cooled to ambient temperature and eoncentrated under reduced pressure to yield a brown oil. The oil was dissolved in $CHCl_3$ (200 mL). The $CHCl_3$ solution was washed with saturated $NaHCO_3$ solution (2 X 50 mL), water (50 mL) and brine (50 mL). The organie portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 18.4 g of *N*-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine as a red/brown foam.

Part F

A solution of *N*-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine (18.4 g, 53.3 mmol) in 100 mL of methanol was placed under an atmosphere of nitrogen and cooled in an ice water bath. The solution was treated with sodium borohydride (2.32 g, 61.3 mmol) over 30 min. The reaction mixture was allowed to slowly come to ambient temperature. After 1.5 h, the reaction was quenched by the addition of 25 mL of saturated NH_4Cl solution. The reaction mixture was concentrated under reduced pressure to remove the methanol. The residue was partitioned between chloroform (150 mL) and 10% Na_2CO_3 solution (35 mL), and the phases were separated. The organic portion was washed with another portion of 10% Na_2CO_3 solution (35 mL), water (35 mL) and brine (35 mL). The organic portion was dried over Na_2SO_4, filtered

and concentrated under reduced pressure to yield a brown foam. The foam was purified by chromatography (SiO_2, 97:3 $CHCl_3$:MeOH gradient to 9:1) to give 16.3 g of *N*-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine as a dark tan solid.

Part G

A solution of *N*-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (9.10 g, 26.2 mmol) in 200 mL of chloroform was placed under an atmosphere of nitrogen and cooled in an ice water bath. The solution was treated with MCPBA (8.28 g, 28.8 mmol, 77% max) and allowed to slowly come to ambient temperature. After 2 h, LC/MS and HPLC indicated complete conversion to the 5-*N*-oxide intermediate. The reaction mixture was again cooled in an ice water bath. The reaction mixture was treated with ammonium hydroxide solution (50 mL, 30%) and stirred vigorously. The mixture was treated with *p*-toluenesulfonyl chloride (5.24 g, 27.5 mmol) and allowed to come to ambient temperature. After 30 min, the reaction was diluted with 50 mL of water, and the phases were separated. The organic portion was washed with water (75 mL), brine (75 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light brown solid. The solid was purified by chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) and then recrystallized from acetonitrile to give 4.52 g of 7-bromo-N^1-isopropyl-2-propyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine as off white crystals. mp 226–228 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (d, J = 8.7 Hz, 1 H), 7.71 (d, J = 2.1 Hz, 1 H), 7.36 (dd, J = 8.7, 2.1 Hz, 1 H), 6.99 (d, J = 1.7 Hz, 1 H), 6.73 (s, 2 H), 3.53-3.40 (m, 1 H), 2.90 (s, 2 H), 1.93-1.80 (m, 2 H), 1.05-1.00 (m, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.9, 152.9, 146.3, 132.5, 127.8, 124.2, 123.5, 123.1, 119.7, 114.0, 79.5, 51.4, 28.2, 21.1, 20.6, 14.3; MS (APCI) *m/z* 362, 364 $(M + H)^+$; Anal. Calcd for $C_{16}H_{20}BrN_5 \cdot 0.25H_2O$: C, 52.40; H, 5.63; N, 19.09; Found: C, 52.03; H, 5.42; N, 19.14.

Part H

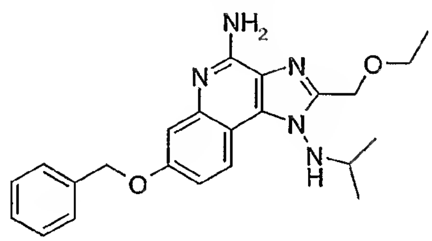
A suspension of 7-bromo-N^1-isopropyl-2-propyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (1.00 g, 2.76 mmol) in 20 mL of 1-propanol was treated with pyridine-3-boronic acid 1,3-propane diol cyclic ester (0.540 g, 3.31 mmol). The head-space of the reaction flask was purged and back-filled with nitrogen (3X). The reaction mixture was then treated with triphenylphosphine (11 mg, 0.041 mmol), sodium carbonate (1.66 mL, 3.31

mmol, 2 M solution in water), water (2 mL) and palladium(II) acetate (3.1 mg, 0.014 mmol). Again the head-space of the reaction flask was purged and back-filled with nitrogen (3X). The reaction was heated to 100° C. After 17 h, the reaction was cooled to ambient temperature and concentrated under reduced pressure to yield a brown solid. The solid was dissolved and partitioned between 15 mL of water and 15 mL of chloroform and then separated. The aqueous portion was extracted with chloroform (2 X 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a tan solid. The solid was purified by chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) and recrystallized from acetonitrile to give 0.515 g of N^1-isopropyl-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine as white crystals.

mp 218–219 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (d, J = 1.7 Hz, 1 H), 8.60-8.57 (m, 2 H), 8.19-8.16 (m, 1 H), 7.88 (d, J = 1.9 Hz, 1 H), 7.61 (dd, J = 8.5, 1.9 Hz, 1 H), 7.53-7.49 (m, 1 H), 7.04 (s, 1 H), 6.59 (s, 2 H), 3.57-3.49 (m, 1 H), 2.92-2.87 (m, 2 H), 1.94-1.82 (m, 2 H), 1.06-1.01 (m, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.8, 152.5, 148.6, 148.1, 145.4, 136.2, 135.4, 134.5, 132.5, 124.5, 124.3, 123.9, 122.2, 119.6, 114.7, 51.3, 28.2, 21.1, 20.6; MS (APCI) *m/z* 361 (M + H)$^+$; Anal. Calcd for $C_{21}H_{24}N_6$: C, 69.97; H, 6.71; N, 23.31; Found: C, 69.78; H, 6.55; N, 23.51.

Example 20

7-Benzyloxy-2-ethoxymethyl-N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A mixture of triethyl orthoformate (92 mL, 0.55 mol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (75.3 g, 0.522 mol) (Meldrum's acid) was heated at 55 °C for 90 minutes and then cooled to 45 °C. A solution of 3-benzyloxyaniline (100.2 g, 0.5029 mol) in methanol (200 mL) was slowly added to the reaction over a period 45 minutes while maintaining the reaction temperature below 50 °C. The reaction was then heated at 45 °C

for one hour, allowed to cool to room temperature, and stirred overnight. The reaction mixture was eooled to 1 °C, and the product was isolated by filtration and washed with cold ethanol (~400 mL) until the filtrate was colorless. 5-{[(3-Benzyloxy)phenylimino]methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione (170.65 g) was isolated as a tan, powdery solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.21 (d, J = 14.2 Hz, 1H), 8.61 (d, J = 14.2 Hz, 1H), 7.49-7.30 (m, 7H), 7.12 (dd, J = 8.1, 1.96 Hz, 1H), 6.91 (dd, J = 8.4, 2.1 Hz, 1H), 5.16 (s, 2H), 1.68 (s, 6H).

Part B

A mixture of 5-{[(3-benzyloxy)phenylimino]methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione (170.65 g, 0.483 mol) and DOWTHERM A heat transfer fluid (800 mL) was heated to 100 °C and then slowly added to a flask containing DOWTHERM A heat transfer fluid (1.3 L, heated at 210 °C) over a period of 40 minutes. During the addition, the reaction temperature was not allowed to fall below 207 °C. Following the addition, the reaction was stirred at 210 °C for one hour, and then allowed to cool to ambient temperature. A precipitate formed, which was isolated by filtration, washed with diethyl ether (1.7 L) and acetone (0.5 L), and dried in an oven to provide 76.5 g of 7-benzyloxyquinolin-4-ol as a tan powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.53 (s, 1H), 7.99 (dd, J = 7.4, 2.4 Hz, 1H), 7.79 (d, J = 7.4 Hz, 1H), 7.50-7.32 (m, 5H), 7.00 (s, 1H), 6.98 (dd, J = 7.4, 2.5 Hz, 1H), 5.93 (d, J = 7.5 Hz, 1H), 5.20 (s, 2H).

Part C

A mixture of 7-benzyloxyquinolin-4-ol (71.47 g, 0.2844 mol) and propionic acid (700 mL) was heated to 125 °C with vigorous stirring. Nitric acid (23.11 mL of 16 M) was slowly added over a period of 30 minutes while maintaining the reaetion temperature between 121 °C and 125 °C. After the addition, the reaction was stirred at 125 °C for 1 hour then allowed to cool to ambient temperature. The resulting solid was isolated by filtration, washed with water, and dried in an oven for 1.5 days to provide 69.13 g of 7-benzyloxy-3-nitroquinolin-4-ol as a grayish powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.77 (s, 1H), 9.12 (s, 1H), 8.17 (dd, J = 6.3, 3.3 Hz, 1H), 7.51-7.33 (m, 5H), 7.21-7.17 (m, 2H), 5.25 (s, 2H).

Part D

A suspension of 7-benzyloxy-3-nitroquinolin-4-ol (75.0 g, 253 mmol), which was made in a separate run, in 500 mL of *N,N*-dimethylformamide was placed under an atmosphere of nitrogen. The suspension was treated with phosphorous oxychloride (27.8 mL, 304 mmol) dropwise over 1.5 h. After 18 h, the reaction mixture was cooled to 0 °C and then poured into 1 L of ice water. The mixture was stirred until the ice had melted. A tan/yellow precipitate was collected by vacuum filtration. The solid was dissolved in dichloromethane (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 71.7 g of 7-benzyloxy-4-chloro-3-nitro-quinoline as an orange solid.

Part E

A solution of *tert*-butyl carbazate (33.1 g, 251 mmol) in 150 mL of dichloromethane was treated with triethylamine (66.5 mL, 502 mmol). The solution was placed under an atmosphere of nitrogen and cooled in a cold-water bath. The solution was treated with a solution of 7-benzyloxy-4-chloro-3-nitroquinoline (71.7 g, 228 mmol) in 350 mL of dichloromethane over 1 h. The reaction was stirred and allowed to warm to ambient temperature. After 15 h, the reaction was diluted with 200 mL of water and 250 mL of $CHCl_3$ and the phases were separated. The organic portion was washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield an orange solid. The solid was recrystallized from dichloromethane to yield 53.5 g of *N'*-(7-benzyloxy-3-nitroquinolin-4-yl)hydrazine *tert*-butyl carboxylate as yellow crystals.

Part F

A solution of *N'*-(7-benzyloxy-3-nitroquinolin-4-yl)hydrazine *tert*-butyl carboxylate (20.00 g, 48.73 mmol) in 200 mL of methanol and 200 mL of acetonitrile was treated with platinum on carbon (2.00 g, 0.51 mmol) and shaken under an atmosphere of hydrogen (3.8×10^5 Pa). After 17 h, the mixture was filtered through a pad of CELITE filter agent and rinsed with MeOH:MeCN (1:1) until the filtrate ran clear. The filtrate was

concentrated under reduced pressure to yield 18.21 g of *N'*-(3-amino-7-benzyloxyquinolin-4-yl)hydrazine *tert*-butyl carboxylate as a red/orange solid.

Part G

A suspension of *N'*-(3-amino-7-benzyloxyquinolin-4-yl)hydrazine *tert*-butyl carboxylate (29.6 g, 77.8 mmol) in 250 mL of 1,2-dichloroethane was placed under an atmosphere of nitrogen. The mixture was treated with triethylamine (30.9 mL, 233 mmol). The mixture was then treated dropwise with ethoxyacetyl chloride (10.5 g, 85.6 mmol). After 2 h, the reaction was concentrated under reduced pressure to give a brown oil. The oil was dissolved in 200 mL of 1-butanol and treated with pyridinium *p*-toluenesulfonate (0.25 g, 1.0 mmol). The mixture was heated to 135 °C under an atmosphere of nitrogen. After 20 h, the reaction mixture was cooled to ambient temperature and concentrated under reduced pressure to give a brown oil. The oil was dissolved in 250 mL of $CHCl_3$ and washed with saturated $NaHCO_3$ solution (75 mL), water (75 mL) and brine (75 mL). The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give an orange/brown oil. The oil was purified by chromatography (SiO_2, 9:1 $CHCl_3$:MeOH) to yield 14.4 g of (7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)*tert*-butyl carbamate as an orange/brown foam.

Part H

A suspension of (7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)*tert*-butyl carbamate (14.4 g, 32.1 mmol) in 100 mL of ethanol was treated with HCl in ethanol (38 mL, 160 mmol, 4.3 M). The mixture was heated to 100 °C under an atmosphere of nitrogen. After 2 h, the reaction mixture was cooled to ambient temperature at which point a solid precipitated from solution. The mixture was diluted with 100 mL of diethyl ether and the solid was triturated for 15 min. The solid was collected by vacuum filtration and washed with several portions of diethyl ether. The solid was dried under vacuum for 2 h. The dry solid was suspended in 150 mL of water and treated with 50% NaOH solution until the pH of the liquid was 12. A brown solid precipitated. The mixture was diluted with 200 mL of CH_2Cl_2 and stirred until the solid dissolved. The layers were then separated. The aqueous portion was extracted with

CH_2Cl_2 (2 X 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 6.91 g of 7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine as a dark tan solid.

Part I

A suspension of 7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (6.91 g, 19.8 mmol) in 55 mL of acetonitrile was treated with 2,2-dimethoxypropane (12.2 mL, 99.2 mmol) and 14 mL of glacial acetic acid. The reaction mixture was heated to 100 °C under an atmosphere of nitrogen. After 22 h, the reaction was cooled to ambient temperature and concentrated under reduced pressure to yield a brown oil. The oil was dissolved in 125 mL of $CHCl_3$ and washed with saturated $NaHCO_3$ solution (2 X 30 mL) and water (30 mL). The combined aqueous washes were back-extracted with $CHCl_3$ (25 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 7.69 g of *N*-(7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine as a brown solid.

Part J

A solution of *N*-(7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine (7.69 g, 19.8 mmol) in 50 mL of methanol was cooled to 0 °C. The solution was treated with sodium borohydride (1.12 g, 29.7 mmol) over 10 min. The reaction was allowed to slowly come to ambient temperature. After 2 h, the reaction was quenched with 15 mL of saturated NH_4Cl solution and concentrated under reduced pressure to yield a tan solid residue. The solid was dissolved in 100 mL of $CHCl_3$ and 25 mL of saturated K_2CO_3 solution then separated. The organic portion was washed with water (25 mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated to yield a brown oil. The oil was purified by chromatography (SiO_2, 98:2 $CHCl_3$:MeOH) to yield 6.63 g of *N*-(7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine as a tan foam.

Part K

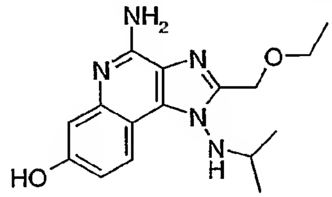
A solution of *N*-(7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (6.63 g, 17.0 mmol) in 90 mL of $CHCl_3$ was treated with MPCBA (6.29

g, 25.5 mmol, 70%). After 3 h, HPLC and LC/MS indicated complete conversion to the intermediate 5-*N*-oxide. The reaction mixture was then treated with concentrated ammonium hydroxide solution (30 mL, 30%). The biphasic reaction mixture was stirred vigorously while *p*-toluenesulfonyl chloride (3.40 g, 17.9 mmol) was added. After 45 min, LC/MS indicated complete conversion to the 4-amine. The reaction mixture was diluted with 30 mL of water and 45 mL of $CHCl_3$ and separated. The organic portion was washed with 10% Na_2CO_3 solution (50 mL) and water (50 mL). The combined aqueous portions were then back-extracted with $CHCl_3$ (25 mL). The combined organic portions were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to yield a tan solid. The solid was purified by chromatography (SiO_2, 96:4 $CHCl_3$:MeOH) to give 5.90 g of 7-benzyloxy-2-ethoxymethyl-N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine as a light tan solid.

mp 194–196 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (d, J = 8.9 Hz, 1 H), 7.50-7.48 (m, 2 H), 7.43-7.38 (m, 2 H), 7.35-7.30 (m, 1 H), 7.09 (d, J = 2.6 Hz, 1 H), 6.96 (dd, J = 9.0, 2.5 Hz, 1 H), 6.91 (d, J = 1.5 Hz, 1 H), 6.57 (s, 2 H), 5.20 (s, 2 H), 4.72 (s, 2 H), 3.64-3.57 (m, 3 H), 1.15 (t, J = 7.0 Hz, 3 H), 1.01 (d, J = 6.1 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.9, 152.6, 149.4, 147.1, 137.7, 133.7, 128.8, 128.1, 128.0, 122.7, 111.8, 109.2, 108.4, 69.5, 65.8, 63.0, 51.6, 20.6, 15.3; MS (APCI) m/z 406 (M + H)$^+$; Anal. Calcd for $C_{23}H_{27}N_5O_2$: C, 68.13; H, 6.71; N, 17.27; Found: C, 68.15; H, 6.91; N, 17.24.

Example 21

4-Amino-2-ethoxymethyl-1-isopropylamino-1*H*-imidazo[4,5-*c*]quinolin-7-ol

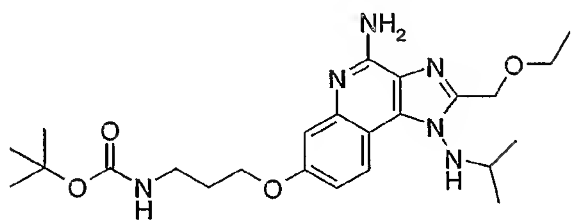


Part A

A solution of 7-benzyloxy-2-ethoxymethyl-N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (1.67 g, 4.12 mmol) in 25 mL of toluene and 25 mL of methanol was treated with palladium on carbon (0.44 g, 0.42 mmol, 10% w/w). The mixture was shaken under an atmosphere of hydrogen (3.8 x 10^5 Pa). After 16 h, the reaction was filtered through a pad of CELITE filter agent and rinsed with solvent until the filtrate ran clear. The filtrate was concentrated under reduced pressure to provide a white solid. Purification by chromatography (SiO_2, 3:1 $CHCl_3$:(80:18:2 $CHCl_3$:MeOH:NH_4OH) gradient to 1:1) gave 0.50 g of 4-amino-2-ethoxymethyl-1-isopropylamino-1*H*-imidazo[4,5-c]quinolin-7-ol as a white solid. MS (APCI) *m/z* 316 $(M + H)^+$.

Example 22

[3-(4-Amino-2-ethoxymethyl-1-isopropylamino-1*H*-imidazo[4,5-c]quinolin-7-yloxy)propyl] *tert*-butyl carbamate



Part A

A solution of di-*tert*-butyl dicarbonate (19.05 g, 87.29 mmol) in tetrahydrofuran (20 mL) was added dropwise to a mixture of 3-amino-1-propanol (6.55 g, 87.2 mmol), tetrahydrofuran (50 mL), and 10% aqueous sodium hydroxide (35 mL). The reaction was stirred for 16 hours. The tetrahydrofuran was removed under reduced pressure, and the residue was adjusted to pH 3 with the slow addition of 15% aqueous potassium hydrogen sulfate. The mixture was extracted with ethyl acetate (3 x), and the combined organic

fractions were washed sequentially with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to provide 16.6 g of *tert*-butyl 3-hydroxypropylcarbamate as a colorless oil containing some residual ethyl acetate.

Part B

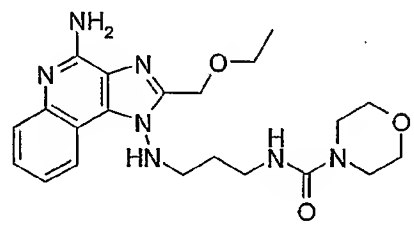
Iodine (21.1 g, 83.1 mmol) was added in three portions to a solution of triphenylphosphine (19.83 g, 75.6 mmol) and imidazole (5.15 g, 75.6 mmol) in dichloromethane (300 mL). The resulting reddish-brown solution with a white precipitate was stirred until all of the iodine had dissolved. A solution of *tert*-butyl 3-hydroxypropylcarbamate (13.25 g, 75.61 mmol) in dichloromethane (150 mL) was added over a period of 45 minutes, and the reaction was stirred for 16 hours at ambient temperature. The reaction mixture was poured into saturated aqueous sodium thiosulfate and stirred until solution became colorless. The organic layer was separated and washed sequentially with saturated aqueous sodium thiosulfate, water, and brine; dried over anhydrous magnesium sulfate; filtered; and concentrated under reduced pressure to a pale yellow oil. The oil was purified by flash column chromatography (eluting with 80:20 hexanes:ethyl aeetate) to a pale yellow oil which slowly crystallizes upon standing to afford 16.2 g of *tert*-butyl 3-iodopropylcarbamate as a yellow solid.

Part C

A solution of 4-amino-2-ethoxymethyl-1-isopropylamino-1*H*-imidazo[4,5-c]quinolin-7-ol (0.11 g, 0.35 mmol) in 10 mL of *N,N*-dimethylformamide was placed under an atmosphere of nitrogen and was treated with cesium carbonate (0.23 g, 0.70 mmol). After 5 min of stirring the mixture was treated with *tert*-butyl 3-iodopropylcarbamate (0.12 g, 0.35 mmol) and heated to 65 °C. After 60 h, the reaction mixture was cooled to ambient temperature and then poured into 100 mL of ice water which resulted in a cloudy suspension. The mixture was extracted with $CHCl_3$ (5 X 25 mL). The combined organic extracts were then washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a tan oil. Chromatography (95:5 $CHCl_3$:(80:18:2 $CHCl_3$:MeOH:NH_4OH) gradient to 1:1 gave 0.040 g of [3-(4-amino-2-ethoxymethyl-1-isopropylamino-1*H*-imidazo[4,5-c]quinolin-7-yloxy)propyl] *tert*-butyl carbamate as a light tan solid. LC/MS (APCI) *m/z* 473 $(M+H)^+$.

Example 23

[3-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-ylamino)propyl]morpholine-4-carboxamide

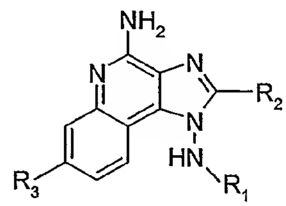


A solution of N^1-(3-aminopropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.500 g, 1.59 mmol) in 10 mL of CH_2Cl_2 was treated with triethylamine (0.443 mL, 3.34 mmol) under an atmosphere of nitrogen and cooled to 0 °C. The reaction mixture was treated dropwise with 4-morpholinecarbonyl chloride (0.065 mL, 0.835 mmol) and allowed to slowly come to ambient temperature. After 60 h, the reaction mixture was quenched with 10% Na_2CO_3 solution, diluted with $CHCl_3$ and the phases were separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light yellow solid. Chromatography (SiO_2, 9:1 $CHCl_3$:(80:18:2 $CHCl_3$:MeOH:NH_4OH) gradient to 1:1) gave a glassy solid. The solid was triturated with diethyl ether and filtered to give 0.046 g of [3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-ylamino)propyl]morpholine-4-carboxamide as a white solid.

mp 158–160 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (d, J = 7.9 Hz, 1 H), 7.58 (d, J = 8.1 Hz, 1 H), 7.46-7.41 (m, 1 H), 7.26-7.21 (m, 1 H), 6.96 (t, J = 5.5 Hz, 1 H), 6.60 (s, 2 H), 6.53 (t, J = 5.1 Hz, 1 H), 4.75 (s, 2 H), 3.61 (q, J = 7.0 Hz, 2 H), 3.50 (t, J = 4.7 Hz, 4 H), 3.22-3.15 (m, 8 H), 1.72 (p, J = 6.9 Hz, 2 H), 1.17 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.0, 152.3, 149.5, 145.3, 132.4, 127.4, 126.1, 124.2, 121.2, 114.7, 66.3, 65.8, 63.1, 50.2, 44.1, 38.3, 28.5, 15.4; MS (APCI) *m/z* 428 $(M + H)^+$; Anal. Calcd for $C_{21}H_{29}N_7O_3$: C, 59.00; H, 6.84; N, 22.93; Found: C, 58.76; H, 7.04; N, 22.82.

Exemplary Compounds

Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (I-1d) and the following R_1, R_2, and R_3 substituents, wherein each line of the table represents a specific compound.



I-1d

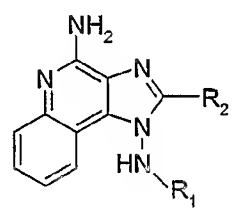
R_1	R_2	R_3
isopropyl	hydrogen	pyridin-3-yl
isopropyl	hydrogen	benzyloxy
isopropyl	hydrogen	2-methanesulfonylaminoethoxy
isopropyl	hydrogen	3-methanesulfonylaminopropoxy
isopropyl	hydrogen	2-(pyridin-3-yl)ethyl
isopropyl	methyl	pyridin-3-yl
isopropyl	methyl	benzyloxy
isopropyl	methyl	2-methanesulfonylaminoethoxy
isopropyl	methyl	3-methanesulfonylaminopropoxy
isopropyl	methyl	2-(pyridin-3-yl)ethyl
isopropyl	propyl	pyridin-3-yl
isopropyl	propyl	benzyloxy
isopropyl	propyl	2-methanesulfonylaminoethoxy
isopropyl	propyl	3-methanesulfonylaminopropoxy
isopropyl	propyl	2-(pyridin-3-yl)ethyl
isopropyl	butyl	pyridin-3-yl
isopropyl	butyl	benzyloxy
isopropyl	butyl	2-methanesulfonylaminoethoxy
isopropyl	butyl	3-methanesulfonylaminopropoxy
isopropyl	butyl	2-(pyridin-3-yl)ethyl
isopropyl	2-methoxyethyl	pyridin-3-yl
isopropyl	2-methoxyethyl	benzyloxy
isopropyl	2-methoxyethyl	2-methanesulfonylaminoethoxy
isopropyl	2-methoxyethyl	3-methanesulfonylaminopropoxy
isopropyl	2-methoxyethyl	2-(pyridin-3-yl)ethyl
isopropyl	ethoxymethyl	pyridin-3-yl
isopropyl	ethoxymethyl	benzyloxy
isopropyl	ethoxymethyl	2-methanesulfonylaminoethoxy
isopropyl	ethoxymethyl	3-methanesulfonylaminopropoxy
isopropyl	ethoxymethyl	2-(pyridin-3-yl)ethyl
benzyl	hydrogen	pyridin-3-yl
benzyl	hydrogen	benzyloxy
benzyl	hydrogen	2-methanesulfonylaminoethoxy

benzyl	hydrogen	3-methanesulfonylaminopropoxy
benzyl	hydrogen	2-(pyridin-3-yl)ethyl
benzyl	methyl	pyridin-3-yl
benzyl	methyl	benzyloxy
benzyl	methyl	2-methanesulfonylaminoethoxy
benzyl	methyl	3-methanesulfonylaminopropoxy
benzyl	methyl	2-(pyridin-3-yl)ethyl
benzyl	propyl	pyridin-3-yl
benzyl	propyl	benzyloxy
benzyl	propyl	2-methanesulfonylaminoethoxy
benzyl	propyl	3-methanesulfonylaminopropoxy
benzyl	propyl	2-(pyridin-3-yl)ethyl
benzyl	butyl	pyridin-3-yl
benzyl	butyl	benzyloxy
benzyl	butyl	2-methanesulfonylaminoethoxy
benzyl	butyl	3-methanesulfonylaminopropoxy
benzyl	butyl	2-(pyridin-3-yl)ethyl
benzyl	2-methoxyethyl	pyridin-3-yl
benzyl	2-methoxyethyl	benzyloxy
benzyl	2-methoxyethyl	2-methanesulfonylaminoethoxy
benzyl	2-methoxyethyl	3-methanesulfonylaminopropoxy
benzyl	2-methoxyethyl	2-(pyridin-3-yl)ethyl
benzyl	ethoxymethyl	pyridin-3-yl
benzyl	ethoxymethyl	benzyloxy
benzyl	ethoxymethyl	2-methanesulfonylaminoethoxy
benzyl	ethoxymethyl	3-methanesulfonylaminopropoxy
benzyl	ethoxymethyl	2-(pyridin-3-yl)ethyl
3-phenylpropyl	hydrogen	pyridin-3-yl
3-phenylpropyl	hydrogen	benzyloxy
3-phenylpropyl	hydrogen	2-methanesulfonylaminoethoxy
3-phenylpropyl	hydrogen	3-methanesulfonylaminopropoxy
3-phenylpropyl	hydrogen	2-(pyridin-3-yl)ethyl
3-phenylpropyl	methyl	pyridin-3-yl
3-phenylpropyl	methyl	benzyloxy
3-phenylpropyl	methyl	2-methanesulfonylaminoethoxy
3-phenylpropyl	methyl	3-methanesulfonylaminopropoxy
3-phenylpropyl	methyl	2-(pyridin-3-yl)ethyl
3-phenylpropyl	propyl	pyridin-3-yl
3-phenylpropyl	propyl	benzyloxy
3-phenylpropyl	propyl	2-methanesulfonylaminoethoxy
3-phenylpropyl	propyl	3-methanesulfonylaminopropoxy
3-phenylpropyl	propyl	2-(pyridin-3-yl)ethyl
3-phenylpropyl	butyl	pyridin-3-yl
3-phenylpropyl	butyl	benzyloxy
3-phenylpropyl	butyl	2-methanesulfonylaminoethoxy
3-phenylpropyl	butyl	3-methanesulfonylaminopropoxy
3-phenylpropyl	butyl	2-(pyridin-3-yl)ethyl
3-phenylpropyl	2-methoxyethyl	pyridin-3-yl
3-phenylpropyl	2-methoxyethyl	benzyloxy
3-phenylpropyl	2-methoxyethyl	2-methanesulfonylaminoethoxy

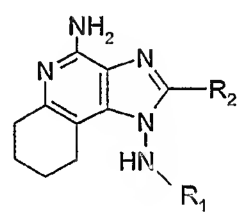
3-phenylpropyl	2-methoxyethyl	3-methanesulfonylaminopropoxy
3-phenylpropyl	2-methoxyethyl	2-(pyridin-3-yl)ethyl
3-phenylpropyl	ethoxymethyl	pyridin-3-yl
3-phenylpropyl	ethoxymethyl	benzyloxy
3-phenylpropyl	ethoxymethyl	2-methanesulfonylaminoethoxy
3-phenylpropyl	ethoxymethyl	3-methanesulfonylaminopropoxy
3-phenylpropyl	ethoxymethyl	2-(pyridin-3-yl)ethyl
3-[3-(2-propyl)ureido]propyl	hydrogen	pyridin-3-yl
3-[3-(2-propyl)ureido]propyl	hydrogen	benzyloxy
3-[3-(2-propyl)ureido]propyl	hydrogen	2-methanesulfonylaminoethoxy
3-[3-(2-propyl)ureido]propyl	hydrogen	3-methanesulfonylaminopropoxy
3-[3-(2-propyl)ureido]propyl	hydrogen	2-(pyridin-3-yl)ethyl
3-[3-(2-propyl)ureido]propyl	methyl	pyridin-3-yl
3-[3-(2-propyl)ureido]propyl	methyl	benzyloxy
3-[3-(2-propyl)ureido]propyl	methyl	2-methanesulfonylaminoethoxy
3-[3-(2-propyl)ureido]propyl	methyl	3-methanesulfonylaminopropoxy
3-[3-(2-propyl)ureido]propyl	methyl	2-(pyridin-3-yl)ethyl
3-[3-(2-propyl)ureido]propyl	propyl	pyridin-3-yl
3-[3-(2-propyl)ureido]propyl	propyl	benzyloxy
3-[3-(2-propyl)ureido]propyl	propyl	2-methanesulfonylaminoethoxy
3-[3-(2-propyl)ureido]propyl	propyl	3-methanesulfonylaminopropoxy
3-[3-(2-propyl)ureido]propyl	propyl	2-(pyridin-3-yl)ethyl
3-[3-(2-propyl)ureido]propyl	butyl	pyridin-3-yl
3-[3-(2-propyl)ureido]propyl	butyl	benzyloxy
3-[3-(2-propyl)ureido]propyl	butyl	2-methanesulfonylaminoethoxy
3-[3-(2-propyl)ureido]propyl	butyl	3-methanesulfonylaminopropoxy
3-[3-(2-propyl)ureido]propyl	butyl	2-(pyridin-3-yl)ethyl
3-[3-(2-propyl)ureido]propyl	2-methoxyethyl	pyridin-3-yl
3-[3-(2-propyl)ureido]propyl	2-methoxyethyl	benzyloxy
3-[3-(2-propyl)ureido]propyl	2-methoxyethyl	2-methanesulfonylaminoethoxy
3-[3-(2-propyl)ureido]propyl	2-methoxyethyl	3-methanesulfonylaminopropoxy
3-[3-(2-propyl)ureido]propyl	2-methoxyethyl	2-(pyridin-3-yl)ethyl
3-[3-(2-propyl)ureido]propyl	ethoxymethyl	pyridin-3-yl
3-[3-(2-propyl)ureido]propyl	ethoxymethyl	benzyloxy
3-[3-(2-propyl)ureido]propyl	ethoxymethyl	2-methanesulfonylaminoethoxy
3-[3-(2-propyl)ureido]propyl	ethoxymethyl	3-methanesulfonylaminopropoxy
3-[3-(2-propyl)ureido]propyl	ethoxymethyl	2-(pyridin-3-yl)ethyl
3-methanesulfonylaminopropyl	hydrogen	pyridin-3-yl
3-methanesulfonylaminopropyl	hydrogen	benzyloxy
3-methanesulfonylaminopropyl	hydrogen	2-methanesulfonylaminoethoxy
3-methanesulfonylaminopropyl	hydrogen	3-methanesulfonylaminopropoxy
3-methanesulfonylaminopropyl	hydrogen	2-(pyridin-3-yl)ethyl
3-methanesulfonylaminopropyl	methyl	pyridin-3-yl
3-methanesulfonylaminopropyl	methyl	benzyloxy
3-methanesulfonylaminopropyl	methyl	2-methanesulfonylaminoethoxy
3-methanesulfonylaminopropyl	methyl	3-methanesulfonylaminopropoxy
3-methanesulfonylaminopropyl	methyl	2-(pyridin-3-yl)ethyl
3-methanesulfonylaminopropyl	propyl	pyridin-3-yl
3-methanesulfonylaminopropyl	propyl	benzyloxy
3-methanesulfonylaminopropyl	propyl	2-methanesulfonylaminoethoxy

3-methanesulfonylaminopropyl	propyl	3-methanesulfonylaminopropoxy
3-methanesulfonylaminopropyl	propyl	2-(pyridin-3-yl)ethyl
3-methanesulfonylaminopropyl	butyl	pyridin-3-yl
3-methanesulfonylaminopropyl	butyl	benzyloxy
3-methanesulfonylaminopropyl	butyl	2-methanesulfonylaminoethoxy
3-methanesulfonylaminopropyl	butyl	3-methanesulfonylaminopropoxy
3-methanesulfonylaminopropyl	butyl	2-(pyridin-3-yl)ethyl
3-methanesulfonylaminopropyl	2-methoxyethyl	pyridin-3-yl
3-methanesulfonylaminopropyl	2-methoxyethyl	benzyloxy
3-methanesulfonylaminopropyl	2-methoxyethyl	2-methanesulfonylaminoethoxy
3-methanesulfonylaminopropyl	2-methoxyethyl	3-methanesulfonylaminopropoxy
3-methanesulfonylaminopropyl	2-methoxyethyl	2-(pyridin-3-yl)ethyl
3-methanesulfonylaminopropyl	ethoxymethyl	pyridin-3-yl
3-methanesulfonylaminopropyl	ethoxymethyl	benzyloxy
3-methanesulfonylaminopropyl	ethoxymethyl	2-methanesulfonylaminoethoxy
3-methanesulfonylaminopropyl	ethoxymethyl	3-methanesulfonylaminopropoxy
3-methanesulfonylaminopropyl	ethoxymethyl	2-(pyridin-3-yl)ethyl

Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (Ii or IIb) and the following R_1 and R_2 substituents, wherein each line of the table is matched with Formula Ii or IIb to represent a specific compound.



Ii



IIb

R_1	R_2
isopropyl	hydrogen
isopropyl	methyl
isopropyl	propyl
isopropyl	butyl
isopropyl	2-methoxyethyl
isopropyl	ethoxymethyl
benzyl	hydrogen
benzyl	methyl
benzyl	propyl
benzyl	butyl
benzyl	2-methoxyethyl
benzyl	ethoxymethyl
3-phenylpropyl	hydrogen
3-phenylpropyl	methyl
3-phenylpropyl	propyl
3-phenylpropyl	butyl

3-phenylpropyl	2-methoxyethyl
3-phenylpropyl	ethoxymethyl
3-[3-(2-propyl)ureido]propyl	hydrogen
3-[3-(2-propyl)ureido]propyl	methyl
3-[3-(2-propyl)ureido]propyl	propyl
3-[3-(2-propyl)ureido]propyl	butyl
3-[3-(2-propyl)ureido]propyl	2-methoxyethyl
3-[3-(2-propyl)ureido]propyl	ethoxymethyl
3-methanesulfonylaminopropyl	hydrogen
3-methanesulfonylaminopropyl	methyl
3-methanesulfonylaminopropyl	propyl
3-methanesulfonylaminopropyl	butyl
3-methanesulfonylaminopropyl	2-methoxyethyl
3-methanesulfonylaminopropyl	ethoxymethyl

CYTOKINE INDUCTION IN HUMAN CELLS

Many compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α in human cells when tested using the method described below. Particular examples include but are not limited to the compounds of Examples 1-18.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", Journal of Leukocyte Biology, 58, 365-372 (September, 1995).

Blood Cell Preparation for Culture:

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation:

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM.

Incubation:

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μM). The final concentration of PBMC suspension is 2×10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation:

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (~200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA:

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

TNF-α INHIBITION IN MOUSE CELLS

Certain compounds of the invention may modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor α (TNF-α) when tested using the method described below.

The mouse macrophage cell line Raw 264.7 is used to assess the ability of compounds to inhibit tumor necrosis factor-α (TNF-α) production upon stimulation by lipopolysaccharide (LPS).

Single Concentration Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 3×10^5 cells/mL in RPMI with 10 % fetal bovine serum (FBS). Cell suspension (100 µL) is added to 96-well flat bottom sterile tissues culture plates (Becton Dickinson Labware, Lincoln Park, NJ). The final concentration of cells is 3×10^4 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 5µM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by a dose response assay.

Incubation

A solution of test compound (1µl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (1 µL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

Dose Response Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 4 x 10^5 cells/mL in RPMI with 10 % FBS. Cell suspension (250 μL) is added to 48-well flat bottom sterile tissues culture plates (Costar, Cambridge, MA). The final concentration of cells is 1 x 10^5 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 0.03, 0.1, 0.3, 1, 3, 5 and 10 μM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by dose response assay.

Incubation

A solution of test compound (200 μl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 μL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF-α Analysis

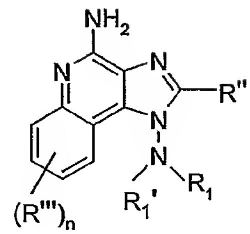
Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource

International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the Formula (I):



I

wherein:

R_1' is selected from the group consisting of hydrogen and alkyl;

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

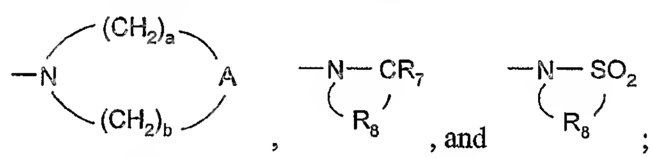
-X-R_5,

-X-N(R_6)-Y-R_4,

-X-C(R_7)-N(R_6)-R_4, and

-X-O-R_4;

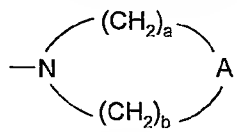
or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl

group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of: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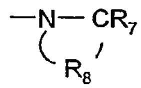
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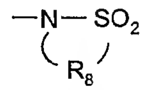
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each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

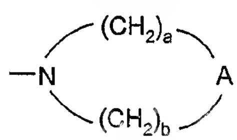
R_7 is selected from the group consisting of =O and =S;

R_8 is C_{2-7} alkylene;

A is selected from the group consisting of -CH(R_6)-, -O-, -N(R_6)-, -N(Y-R_4)-, and -N(X-N(R_6)-Y-R_4)-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_7)-, -C(R_7)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_6)-, and -C(R_7)-N(R_9)-; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group


;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_6)-, -N(Y-R_4)-, or -N(X-N(R_6)-Y-R_4)- then a and b are independently integers from 2 to 4;

each R" is independently hydrogen or a non-interfering substituent;

each R''' is independently a non-interfering substituent; and

n is an integer from 0 to 4;

or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1 wherein the compound induces the biosynthesis of one or more cytokines.

3. The compound or salt of claim 1 wherein R" is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

$-N(R_6)_2$,

$-C(R_7)-N(R_6)_2$,

$-S(O)_2-N(R_6)_2$,

$-N(R_6)-C(R_7)-C_{1-10}$ alkyl,

$-N(R_6)-S(O)_2-C_{1-10}$ alkyl,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

-aryl,

-heteroaryl,

-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

each R_7 is independently selected from the group consisting of =O and =S; and

Z is selected from the group consisting of -O- and $-S(O)_{0-2}-$.

4. The compound or salt of claim 1 wherein:

R''' is R or R_3 when n is 1, R or one R and one R_3 when n is 2, or R when n is 3 to 4;

R is selected from the group consisting of alkyl, alkenyl, alkoxy, halogen, fluoroalkyl, hydroxy, amino, alkylamino, and dialkylamino;

R_3 is selected from the group consisting of:

-Z'-R_4',

-Z'-X'-R_4',

-Z'-X'-Y'-R_4', and

-Z'-X'-R_5';

Z' is a bond or -O-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene, or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_{11})-,

-C(R_7)-,

-C(R_7)-O-,

-O-C(R_7)-,

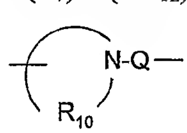
-O-C(O)-O-,

-N(R_{11})-Q-,

-C(R_7)-N(R_{11})-,

-O-C(R_7)-N(R_{11})-,

-C(R_7)-N(OR_{12})-,



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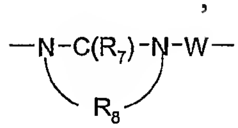

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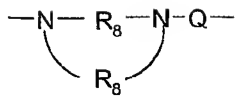

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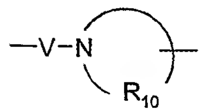

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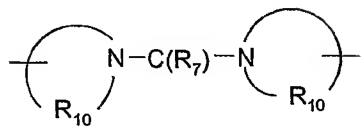

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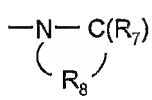
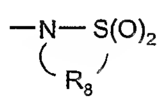
R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, eyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

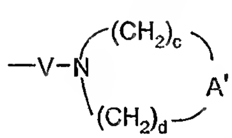
R_5' is selected from the group consisting of:



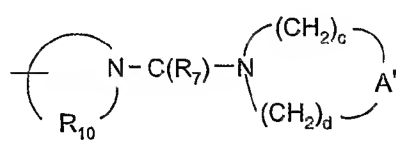
,



,



, and



;

each R_7 is independently selected from the group consisting of =O and =S;

each R_8 is independently C_{2-7} alkylene;

R_{10} is C_{3-8} alkylene;

each R_{11} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxyC_{2-10} alkylenyl, and arylC_{1-10} alkylenyl;

R_{12} is selected from the group consisting of hydrogen and alkyl;

A' is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4')-$;

Q is selected from the group consisting of a bond, $-C(R_7)-$, $-C(R_7)-C(R_7)-$,

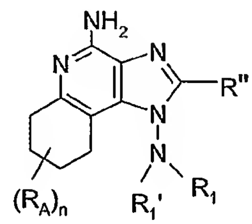
$-S(O)_2-$, $-C(R_7)-N(R_{11})-W-$, $-S(O)_2-N(R_{11})-$, $-C(R_7)-O-$, and $-C(R_7)-N(OR_{12})-$;

V is selected from the group consisting of $-C(R_7)-$, $-O-C(R_7)-$, $-N(R_{11})-C(R_7)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

c and d are independently integers from 1 to 6 with the proviso that $c + d$ is ≤ 7, and when A' is -O- or $-N(R_4')-$ then c and d are independently integers from 2 to 4.

5. A compound of the Formula (II):



II

wherein:

each R_A is independently selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio,

$-NH_2$,

-NH(alkyl), and

$-N(alkyl)_2$;

n is an integer from 0 to 4;

R_1' is selected from the group consisting of hydrogen and alkyl;

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,